



STUDIES ON THE SCOPE OF ACID- CATALYSED CYCLISATION
REACTIONS OF ORTHO- SUBSTITUTED NITROAROMATIC
DERIVATIVES TO N-HYDROXY HETEROCYCLES AND
RELATED COMPOUNDS

by

David Gordon Tredgett B.Sc.

Thesis presented for the degree of Doctor of Philosophy

University of Edinburgh

2000



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DECLARATION

I declare that this thesis is my own composition, the work of which is a record that has been carried out by myself and that it has not been submitted in any previous application for a higher degree.

The thesis describes the results of research carried out in the Department of Chemistry, University of Edinburgh, under the supervision of Dr.G.Tennant between October 1996 and September 1999.

Signed

Date

31/12/00

ACKNOWLEDGEMENTS

I would like to thank Dr.G.Tennant for his supervision and encouragement during the course of my research.

I would like to thank the University of Edinburgh for the provision of laboratory and library facilities and EPSRC for the funding for this research.

I would also like to acknowledge the help and expertise of the technical staff of the Department of Chemistry, University of Edinburgh and especially Dr.S.Parsons for carrying out the X-ray analysis.

Finally, I am grateful to my mum, gran, brother and of course Annie for all their help and support over the last 4 years.

POSTGRADUATE LECTURE COURSES ATTENDED

(October 1996 - September 1999)

“Protecting and Commercialising Inventions” – 1997; Dr.R.Pugsley, Dr.J.Brennan, Dr.S.C.Stephen, Dr.K.Winton, and Dr.J.D.R.Vass (Zeneca Specialties, Manchester).

“Drug Discovery” – 1997; Dr.H.Broughton, Dr.L.Castro and Dr.G.Stevenson (Merck, Sharp and Dohme).

“Highlights of Organic Chemistry” – 1997; Dr.I.Gosney, Dr.A.Hulme, Dr.H.McNab, Dr.R.M.Paton and Prof.N.Turner (University of Edinburgh).

“Good Housekeeping and Working Practices” – 1998; Mr.S.Spittle (HSE Adviser, Merck Ltd., Poole, Dorset).

“Synthons in Organic Chemistry” – 1998; Prof.E.Vilsmaier.

“Modern Aspects of NMR Spectroscopy” Part 1– 1998; Dr.J.Parkinson, Dr.D.Reed, Dr.I.Sadler, Prof.P.Sadler, Dr.D.Uhrin (University of Edinburgh).

“Modern Aspects of NMR Spectroscopy” Part 2– 1998; Dr.J.Parkinson, Dr.D.Reed, Dr.I.Sadler, Prof.P.Sadler, Dr.D.Uhrin (University of Edinburgh).

“Medicinal Chemistry” – 1998; Various Lecturers (Merck, Sharp and Dohme).

“Current Awareness in Organic Chemistry” – 1999; Dr.G.S.McDougall, Dr.H.McNab, Dr.R.M.Paton, Dr.G.Tennant, and Prof.N.Turner (University of Edinburgh).

Departmental Seminars and Colloquia: 1996-97; 1997-98; 1998-99.

ABSTRACT

The subject matter of this thesis is concerned with investigations on the novel acid-catalysed cyclisation reactions of ortho- substituted nitroaromatic derivatives to N-oxygenated quinolinones and related heterocycles. The description of the results obtained in these studies is preceded in Chapter 1 by a survey of the known acid-catalysed cyclisation reactions of ortho substituted nitroaromatic derivatives to N-oxygenated heterocycles and the potential biological properties of such N-oxygenated heterocyclic derivatives.

Chapter 2 describes investigations on the synthesis of N-hydroxyquinolinone derivatives by the acid- catalysed cyclisation reactions of ortho- substituted nitrobenzene derivatives. In particular, these studies were concerned with substituent effects para to the ortho- side- chain in nitrobenzene derivatives in respect of the efficiency of their cyclisation to N-hydroxyquinolinone derivatives in the presence of hydrogen chloride. Subsequent studies on the reactivity of the N-hydroxyquinolinone derivatives are also reported in this Chapter. Investigations were also carried out on the Lewis acid catalysed cyclisation reactions of *trans* 2-benzoyl-3-(2-nitrophenyl)oxirane derivatives to novel 2,1-benzisoxazolone derivatives.

Chapter 3 describes the efficient synthesis of novel N-hydroxybenzoquinolinone derivatives by the hydrogen chloride catalysed cyclisation reactions of 2-nitronaphthylidene derivatives as well as investigations of the reactivity of the N-hydroxy heterocycles so produced. Studies seeking to extend this work to the synthesis of N-hydroxythienopyridinones and N-hydroxyimidazopyridinones by the acid- catalysed cyclisation reactions of the corresponding nitrothienylidene and nitroimidazolylidene derivatives are also reported. Also described in this Chapter are studies on the hydrogen chloride and Lewis acid- catalysed cyclisation reactions of 2-nitronaphthyloxirane, 2-nitrothienyloxirane and 5-nitroimidazolyloxirane derivatives, in the case of the Lewis acid promoted processes to afford naphthisoxazolone, thienoisoxazolone and imidazoisoxazolone derivatives.

PREFACE

Ortho- substituted nitroaromatic derivatives are of interest because of their utility as intermediates in the synthesis of N-hydroxy heterocycles which have potentially important biological properties eg certain N-oxygenated heterocycles are known to have antibiotic activity and also exhibit radio sensitising properties, important in the treatment of certain cancer tumour cells.

Ortho- substituted nitrobenzene derivatives are converted into N-hydroxyquinolinone derivatives in the presence of hydrogen chloride. Cyclisation reactions of this type frequently lead to N-oxygenated heterocycles with unambiguous N-oxygenation and/or unusual substitution patterns.

These interesting and potentially important properties prompted investigations on synthetic routes to ortho- substituted nitroaromatic derivatives and their subsequent conversion (in the presence of hydrogen chloride) into novel or otherwise difficult to obtain N-hydroxy heterocycles.

The results of these investigations are reported in the following thesis and, by way of introduction, are preceded by a literature survey of the biological properties of N-oxygenated heterocycles and their synthesis by acid- catalysed cyclisation of ortho- substituted nitroaromatic derivatives.

CHAPTER 1

A SURVEY OF THE BIOLOGICAL PROPERTIES OF N-OXYGENATED HETEROCYCLES AND THEIR SYNTHESIS BY ACID- CATALYSED CYCLISATION OF ORTHO- SUBSTITUTED NITROAROMATIC COMPOUNDS

A SURVEY OF THE BIOLOGICAL PROPERTIES OF N- OXYGENATED HETEROCYCLES AND THEIR SYNTHESIS BY ACID- CATALYSED CYCLISATION OF ORTHO- SUBSTITUTED NITROAROMATIC COMPOUNDS

1. INTRODUCTION

The object of this introductory chapter is to summarise the biological properties of N-oxygenated heterocycles and to comment on their synthesis specifically by acid-catalysed cyclisation of ortho- substituted nitrobenzene derivatives. The scope of such cyclisation reactions has been covered in two review articles.^{1,2} This chapter will provide an overview of acid- catalysed cyclisation reactions of ortho- substituted nitroaromatic derivatives involving the direct interaction of the nitro- group with the ortho- side- chain.

2. BIOLOGICAL PROPERTIES OF N-OXYGENATED HETEROCYCLES

2.1 Antibiotic and Antiviral Properties

Interest in the biological effects of heteroaromatic N- oxides was first stimulated in 1938 by the isolation (Figure 1) from the organism *Chromobacterium iodinum* of the dihydroxyphenazine-N,N-dioxide (iodinin)(1) which exhibited strong antibacterial activity.³ Later studies (Figure 1) showed that quinoxaline-1,4-di-N-oxides

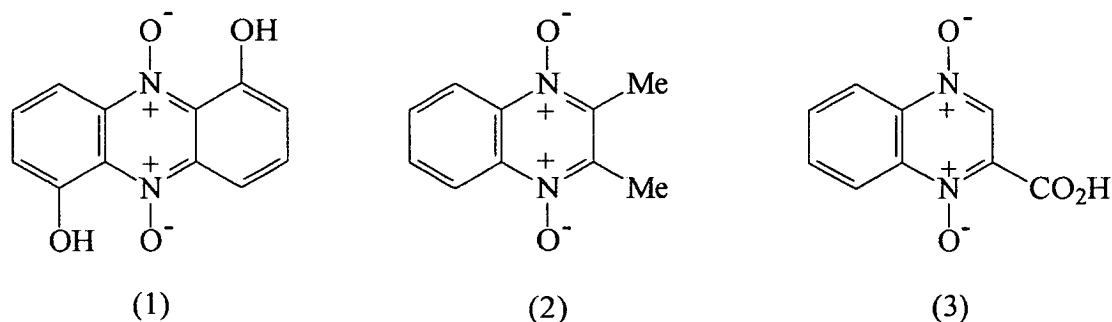
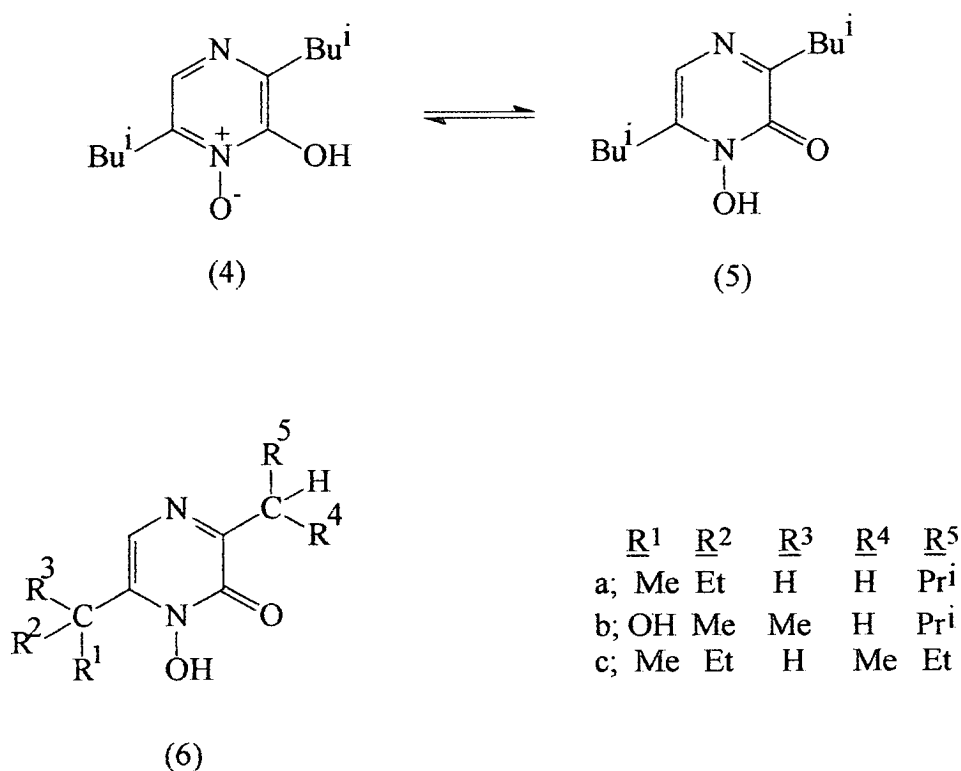


Figure 1

such as the 2,3-dimethyl derivative (2) or the 2-carboxylic acid (3) were also antibacterial agents particularly for Gram negative bacteria such as *Salmonella dublin*.⁴ Quinoxaline-2-carboxylic acid 1,4-di-N-oxide (3), isolated from *Streptomyces ambrofaciens*, was found to exhibit higher *in vivo* than *in vitro* antibacterial properties with activities two orders of magnitude higher under anaerobic conditions.⁵ The quinoxaline-1,4-di-N-oxide derivative (3) may in fact be a pro- drug⁵ since the active form has not yet been identified.

Aspergillic acid, isolated from *Aspergillus flavus* by White and Hill⁶ in 1943, is an antibiotic which inhibits the growth of Gram negative and Gram positive bacteria. This N- oxygenated heterocycle (Scheme 1) exists in two tautomeric forms, namely 3,6-diisobutyl-2-hydroxypyrazine 1-N-oxide (4) and 1,2-dihydro-3,6-diisobutyl-1-hydroxy-2-oxypyrazine (5).



Scheme 1

Antibiotic properties are generally exhibited (Scheme 1) by N-hydroxypyrazinones (6)⁷ structurally related to aspergillic acid. The oxygenated nitrogen atom was found to be an essential feature for the potency of these compounds as antibacterial agents. Deoxygenated compounds related to aspergillic acid were shown to have only weak antibacterial activity.⁸

Oxoquinolones (Figure 2), such as 1-methyl-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (7), are also important antibiotics.⁹ Micro-organisms have the ability to rapidly mutate and so become more resistant to traditional antibiotics (eg penicillins, cephalosporins). New antibiotics are therefore required to combat resistant micro-organisms. The discovery during the early 1980's of these

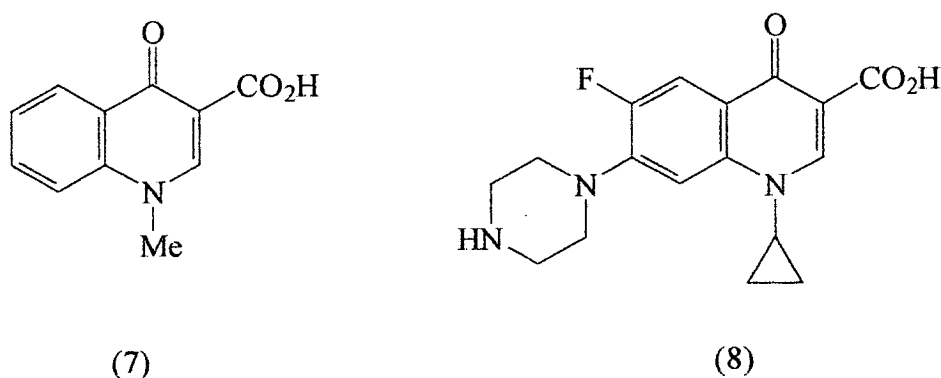
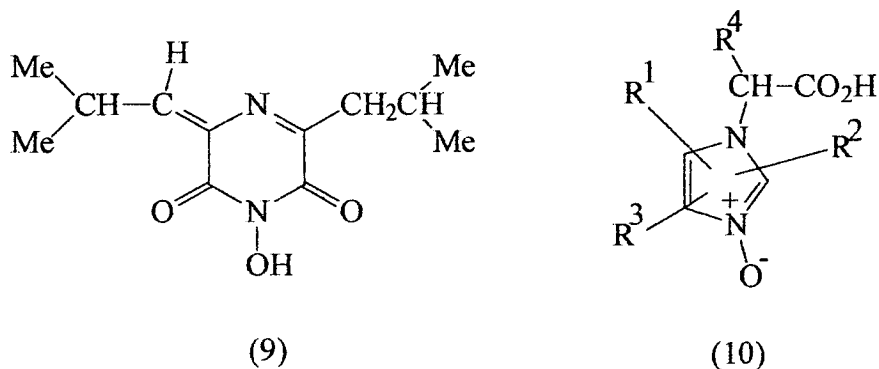


Figure 2

oxoquinoline antibiotics culminated (Figure 2) in the discovery of the extremely effective compound, ciprofloxacin (8), which has a wide range of antibiotic activity.¹⁰ The 4-oxoquinoline group of antibiotics operate by inhibiting the enzyme DNA gyrase. This enzyme is responsible for the winding of the DNA helix into the supercoiled form. However the precise way in which the inhibition of DNA gyrase relates to the antimicrobial effects is not understood.¹⁰ As discussed later acid-catalysed cyclisation of ortho- substituted nitroaromatic compounds provides a synthetic route to N-hydroxy-4-oxoquinoline derivatives with potential antibiotic activity.

Endonucleases are enzymes which cause unwinding of the DNA helix from the supercoiled form. These enzymes are required by viruses so that replication can occur. Recent work¹¹⁻¹⁴ has shown (Figure 3) that N-hydroxydioxopyrazine derivatives [eg (9)] are endonuclease inhibitors and so can function as antiviral agents.



[R¹, R², R³= H or alkyl; R⁴= alkyl, hydroxyalkyl]

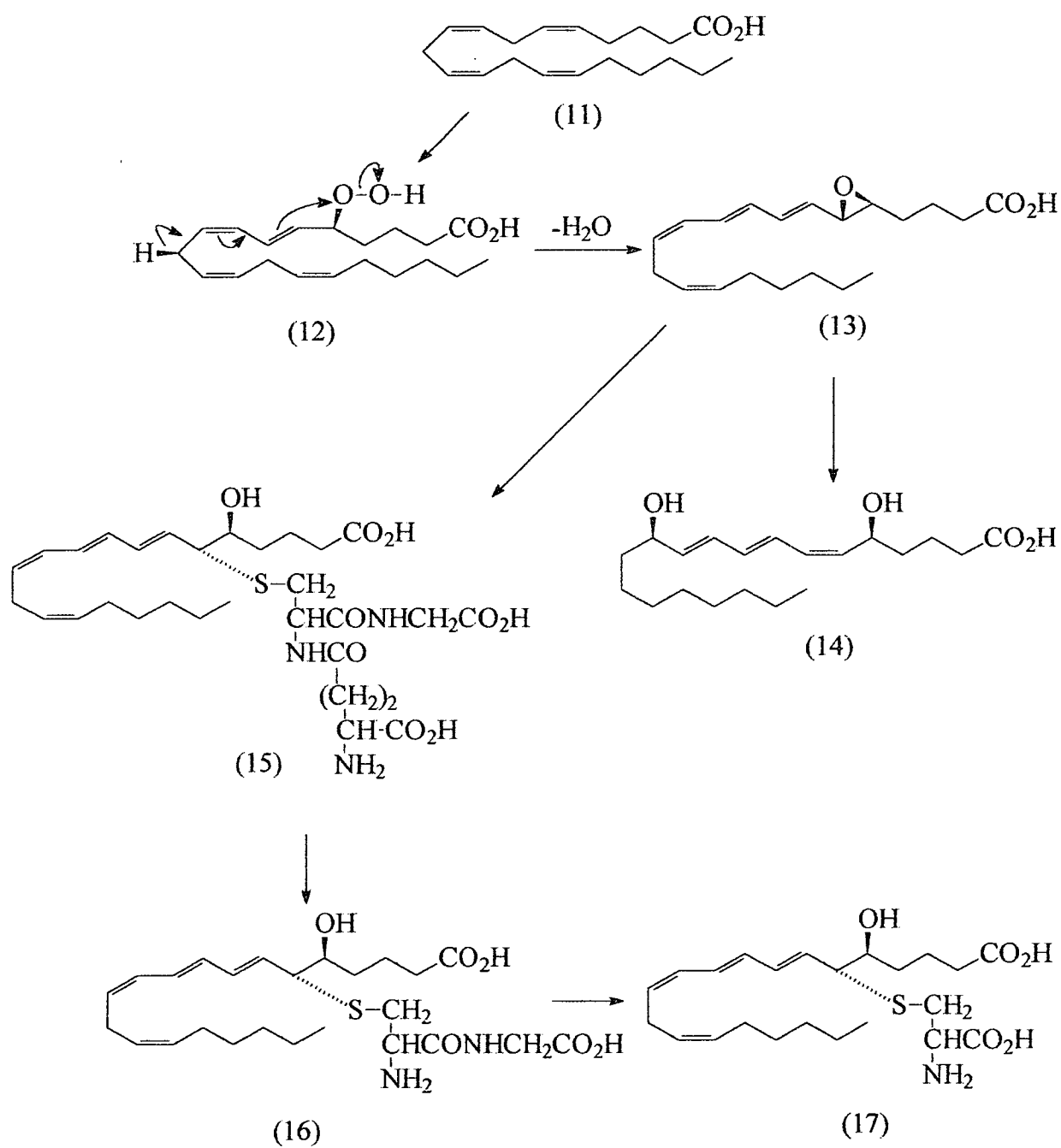
Figure 3

Antiviral activity is also exhibited by five- membered N-oxygenated heterocycles (Figure 3). Imidazole-3-oxide derivatives (10) are known¹⁵ to be virucides against phytopathogenic viruses (eg Lucerne mosaic virus, potato X virus). Antiviral agents of this type would be particularly useful to the agrochemical industry.

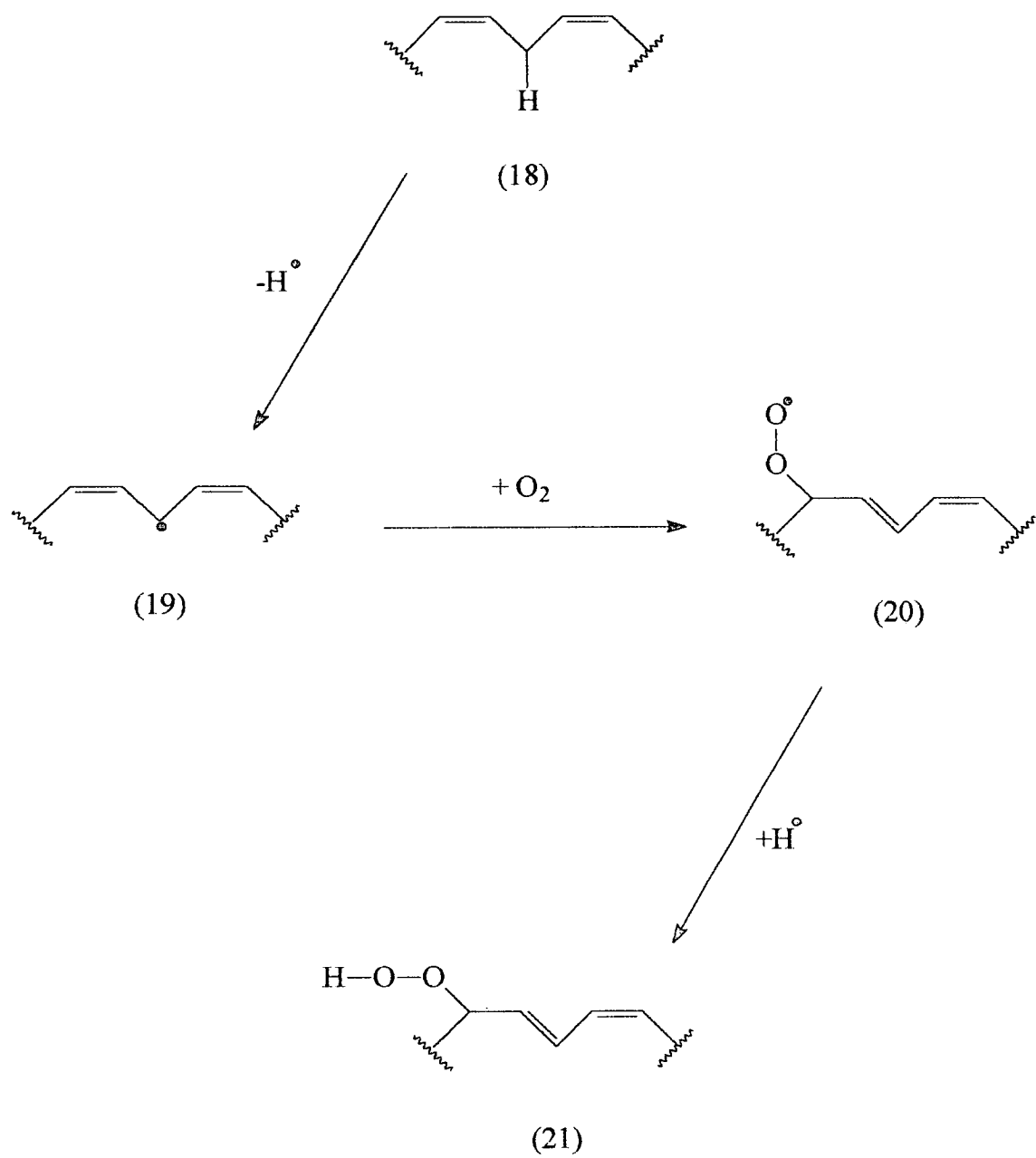
2.2 Antiinflammatory Agents

Unwanted hydroxyl and superoxide radicals promote inflammation and arthritis.¹⁶⁻¹⁹ Excessive swelling can occur due to hydroxyl and superoxide radicals around the cartilage in joints and as a consequence results in impeded movement of the bones (arthritis). Hydroxyl and superoxide radicals bring about inflammation in the cell lining in smooth muscle located in the bronchia. Such inflammation causes restriction of the airway and breathing becomes more difficult (asthma).

An imbalance in the body's natural chemistry can cause excessive amounts of hydroxyl and superoxide radicals to be present. This abnormally high concentration



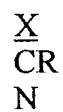
Scheme 2



Scheme 3

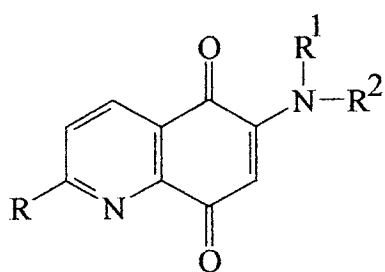
of radicals initiates the body's defence mechanism which involves the formation of substances known as leukotrienes. The effects of inflammation and swelling in the cartilage and smooth muscle are due directly to the presence of leukotrienes which are synthesised by different types of cells. Leukotrienes are recognised to be the components of the slow reacting substances of anaphylaxis released from sensitised lung cells after immunological challenge and act at very low concentrations (as low as 10^{-10} M) to contract vascular, respiratory, and intestinal smooth muscle. In this respect they are known to be ~10,000 fold more potent than histamine, which is a stimulant of allergic reactions. Thus (Scheme 2), 5-HPETE (12) (5-hydroperoxyeicosatetraenoic acid), a substance which is not a physiological mediator, is converted by enzymes in a series of reactions into leukotrienes.²⁰ The first reaction in this sequence is the initial formation of 5-HPETE (12) by the oxidation of arachidonic acid (11) which is catalysed by the enzyme lipoxygenase. The mechanism [Scheme 3; (18)→→(21)] of this reaction is thought to involve a hydrogen radical abstraction from a 1,4-pentadiene unit. This is followed by addition of oxygen and then re-addition of the hydrogen radical. The cascade of reactions continues with 5-HPETE (12) being converted into an unstable epoxide, leukotriene A₄ (13). Glutathione-S-transferase then catalyses the addition of the glutathione sulfhydryl group to the epoxide (13), forming the first of the leukotrienes, leukotriene C₄ (15). γ -Glutamyltransferase removes glutamic acid, thus modifying leukotriene C₄ (15) to leukotriene D₄ (16). Leukotriene D₄ (16) is subsequently transformed into leukotriene E₄ (17) by a dipeptidase that eliminates glycine. Leukotriene A₄ (13) can also be converted into leukotriene B₄ (14) by the enzyme leukotriene A₄ hydrolase. Leukotriene B₄ (14) is a potent chemotactic agent involved in attracting certain types of white blood cells to fight infection. To override this cascade of reactions (Scheme 2) which causes inflammation it is necessary to inhibit the enzyme lipoxygenase. Lipoxygenase belongs to a family of enzymes which have closely related structures. Hence any drug synthesised to inhibit lipoxygenase must be structure specific so that other similar enzymes, where inhibition is not required, are not suppressed.

Known inhibitors (Figure 4) of lipoxygenase are quinone derivatives (22), which are oxy- radical scavengers.²¹ However a range of drugs can react with hydroxyl and

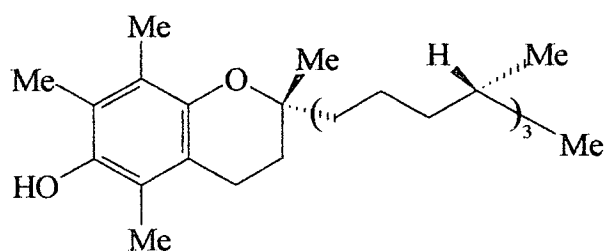


Scheme 4

superoxide radicals. Chemotherapeutic quenching of these radicals will occur if the reaction products are non-toxic to the body. The efficiency of chemotherapeutic quenching depends upon the radical trap being regenerated *in vivo* so that high concentrations of drug need not be administered. The body's natural antioxidant (Figure 4) α -tocopherol (vitamin E) (23) has been shown²² to scavenge one hundred and twenty singlet oxygen radicals before breakdown occurs. An attractive possibility for antiinflammatory agents would therefore be molecules with a turnover capability comparable to that of α -tocopherol (23) while incorporating the structural features of quinone derivatives such as (22). Possible candidate molecules might incorporate (Scheme 4) heterocyclic N-hydroxy diosphenol structures (24) capable of turnover through the redox interconversions [(24) \rightleftharpoons (25) \rightleftharpoons (26) \rightleftharpoons (27)]. As



(22)



(23)

[R,R¹,R² = H or alkyl]

Figure 4

will be discussed later heterocyclic N-hydroxy diosphenol derivatives of general structural type (24) are synthetically accessible via the acid-catalysed cyclisation of ortho-substituted nitroaromatic derivatives. Provided a reduction step in the sequence of interconversions shown in Scheme 4 could be adapted to occur *in vivo* N-hydroxy diosphenol structures (24) should have the turnover capability required of efficient radical scavengers. Heterocyclic N-hydroxy diosphenols of general structure (24) might therefore function as useful antiinflammatory agents.

2.3 Hypoxic- Cytotoxic / Anticancer Properties

The term 'cytotoxic drug' applies to any drug that can damage or kill cells. In practice however the term is used in the more restrictive sense of drugs that inhibit cell division and are potentially useful in cancer chemotherapy. Cytotoxic agents are antiproliferative with regard to cell division in a localised area but they have no effect on cancer spreading into tissues in other layers. Cytotoxic agents also do not inhibit secondary tumours that have formed in other regions of the body due to migration of cancerous cells.

Malignant (cancerous) cells undergo rapid cell division and as a result the cells within the centre of a solid tumour are oxygen deficient. The result is that radiation therapy using X- rays is limited in its effectiveness because it is reliant on the concentration of molecular oxygen within the cells. Tumours therefore have a tendency to regenerate because the hypoxic cells recover from the radiation treatment.^{23,24}

Electron poor agents (Figure 5) such as misonidazole (28), can differentially sensitise hypoxic cells to X- rays.²⁵ The mode of action of such agents is based on their conversion into radical species and other toxic intermediates such as nitrosamines by enzymes (nitro reductases) contained within hypoxic cells. Nitrosamines so produced scavenge intracellular thiols and the resulting interference with the repair mechanism of the hypoxic cells leaves them susceptible to radiation therapy. Unfortunately, electron poor agents such as misonidazole (28) are unacceptably neurotoxic

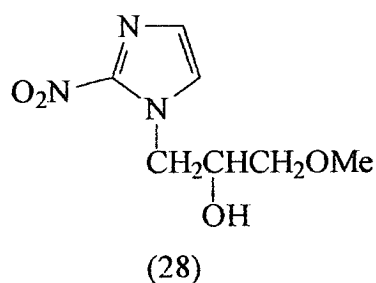


Figure 5

at the dosage levels required for optimal hypoxic cell radiosensitisation. An alternative approach would be to utilise, in combination with radiation therapy, compounds that selectively kill radiation resistant hypoxic tumour cells. Cytotoxic agents (Figure 6) such as benzo-1,2,4-triazine-1,4-di-N-oxide (29) and the related N-oxides (30) and (31) are active in this respect both *in vitro* and *in vivo*.²⁶⁻²⁸ Also quinoxin (30) becomes potently cytotoxic when bio-reduced within the organism.²⁹ Unfortunately, however, quinoxin (30) has been reported³⁰ to be mutagenic. In contrast structurally related compounds (Figure 6) (32) and (33) retain their cytotoxic activity but are no longer mutagenic.³¹

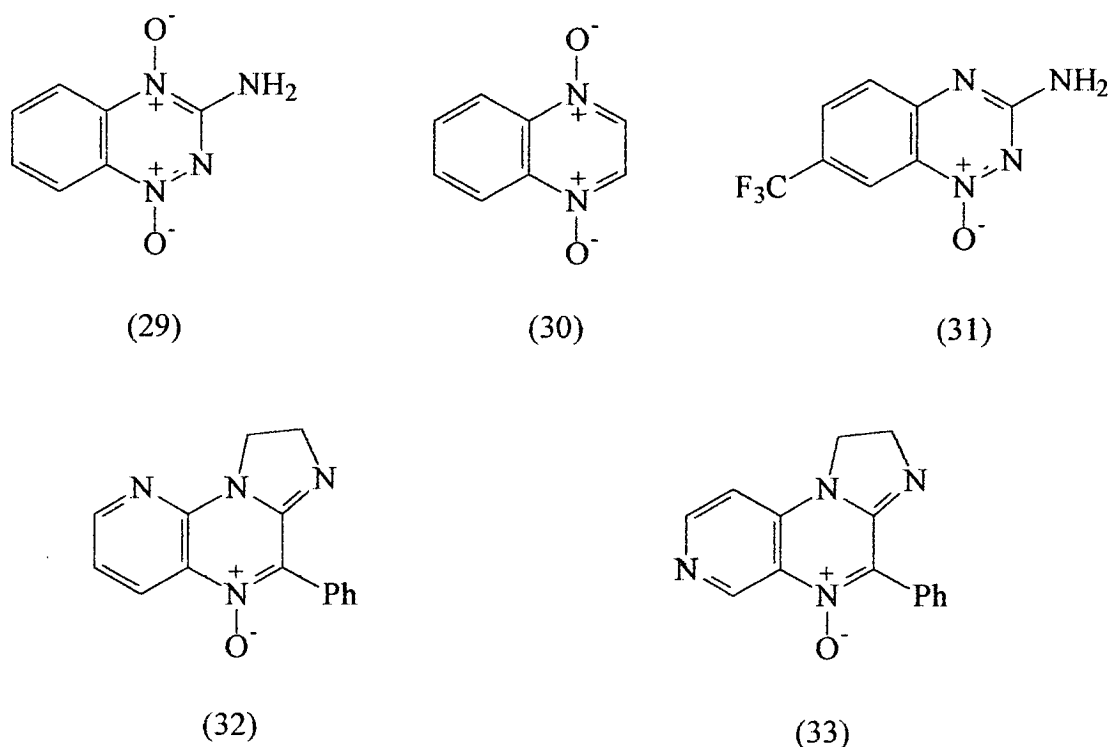


Figure 6

Recently (Figure 7) benzofuroxans such as the methoxy derivative (34) and hydroxamic acid derivatives of quinoxaline di-N-oxides (35) have been found³² to have hypoxic- cytotoxic activity.

N-Oxygenated purine nucleosides (Figure 7), such as guanosine 7-N-oxide (36) (synthesised from guanine-7-N-oxide and ribose 1-phosphate using a cell suspension of *Bacillus subtilis*) have been shown³³ to be anticancer agents. The purine

nucleoside (36) enters the target cell and undergoes the same phosphorylation reactions as the physiological nucleoside. The precise pathway (or pathways) by which the abnormal nucleotide acts as an anticancer agent has not been identified. However, the cytotoxic effects are probably the result of the nucleoside (36) being involved in a number of biological processes within the cell.

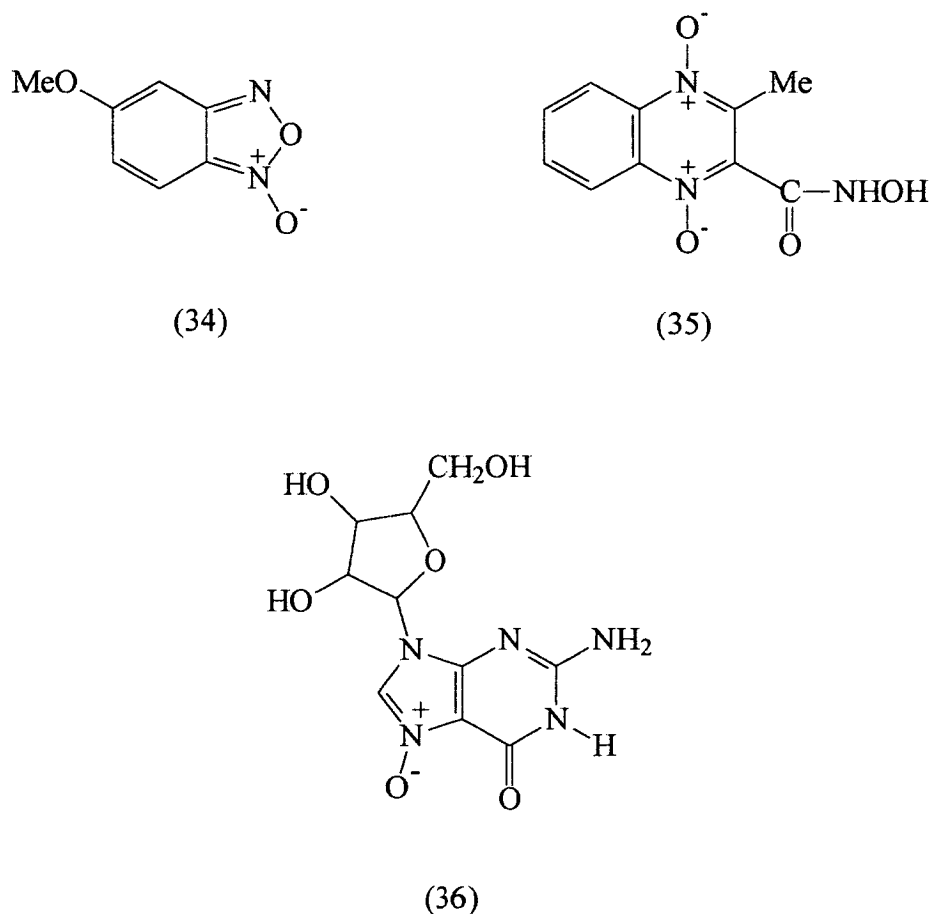
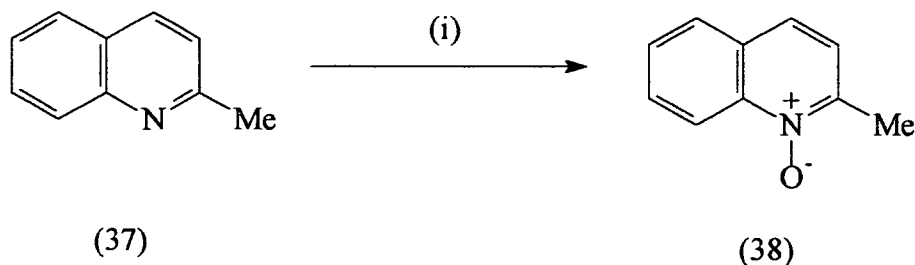


Figure 7

3. THE SYNTHESIS OF N-OXYGENATED HETEROCYCLES BY ACID-CATALYSED CYCLISATION OF ORTHO- SUBSTITUTED NITROAROMATIC COMPOUNDS

The simplest and most generally applicable method for the synthesis of heterocyclic N- oxides involves direct peracid oxidation of the parent heterocycle (Scheme 5),

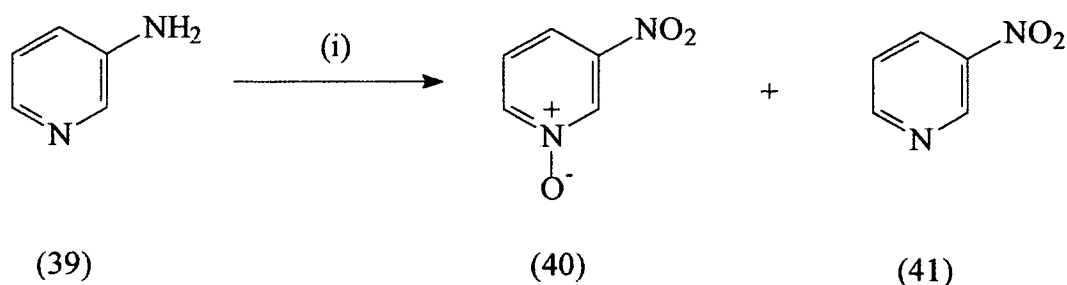
such as the conversion³⁴ of quinaldine (37) into quinaldine N-oxide (38) using perbenzoic acid. However this approach is unsatisfactory in the case of polyazaheterocycles due to a lack of regioselectivity in the particular nitrogen atom oxidised and also for nitrogen heterocycles containing substituents sensitive to oxidation. The latter drawback is illustrated³⁵ by the transformation (Scheme 6) of



(i) PhCO_3H , benzene, room temp.

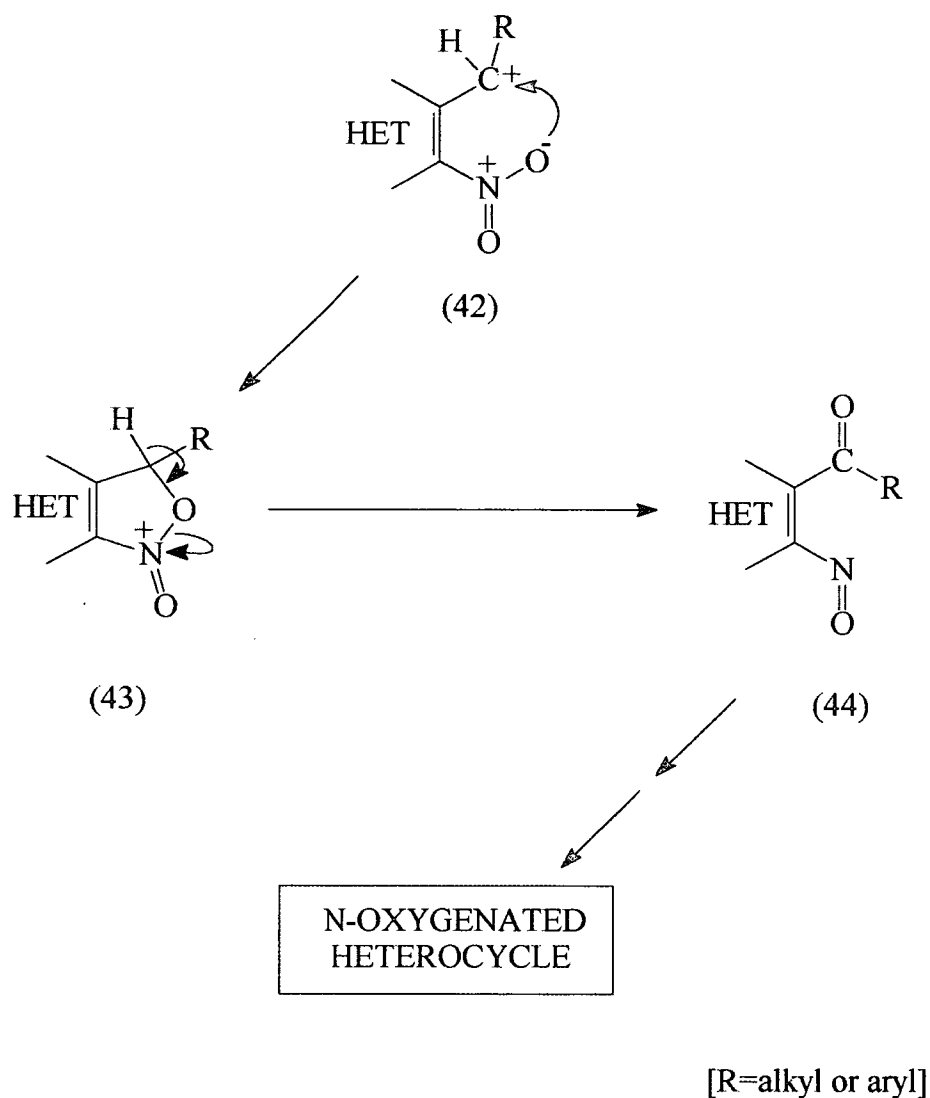
Scheme 5

3-aminopyridine (39) into the N-oxide (40), wherein the amino group has also been oxidised to a nitro group. Some of the deoxygenated nitropyridine derivative (41) is also isolated in this reaction.



(i) $\text{CF}_3\text{CO}_3\text{H}$, H_2O_2 , heat.

Scheme 6



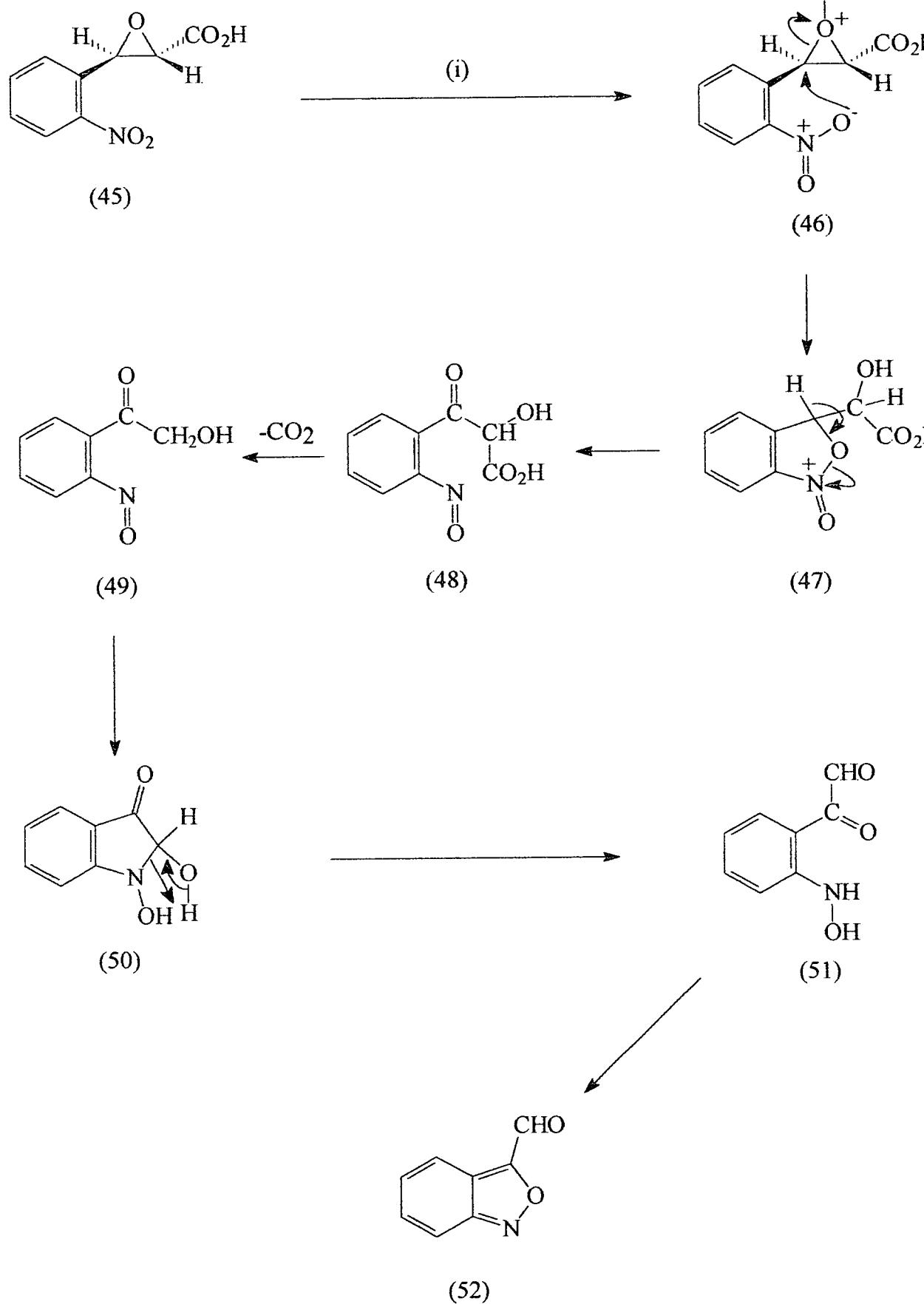
Scheme 7

The synthetic route under investigation in the present studies involves the electrophilic cyclisation of ortho- substituted nitroaromatic derivatives. This general synthetic approach has features which make it superior to direct peracid oxidation of the parent heterocycle. The electrophilic cyclisation of ortho- substituted nitroaromatic derivatives is regiospecific with respect to the location of the N-oxide substituent in the ultimate heterocyclic N-oxide product. Also other substituents sensitive to oxidation (eg amino group) contained within the nitroaromatic derivative remain unaffected by this method of heterocyclic N-oxide formation.

Electrophilic cyclisation reactions of ortho- substituted nitroaromatic derivatives to produce N- oxygenated heterocycles can be viewed as occurring by the general mechanism shown in Scheme 7. This involves the nitro- group behaving as a nucleophile and reacting via the negatively charged oxygen atom with an electron poor (electrophilic) centre in the side- chain to form, via the cyclic intermediate (43), an ortho- nitroso carbonyl derivative (44). This can undergo further reaction in a variety of ways often though not always leading to an N-oxygenated heterocyclic product. Previous reviews^{1,2} of the literature concerning electrophilic cyclisation reactions of ortho- substituted nitroaromatic derivatives illustrate the synthetic utility of such reactions. Cyclisation reactions of this type produce N-oxygenated heterocycles of pre-determined orientation of the N-oxide group from which the parent heterocycle can also be obtained by subsequent reduction.

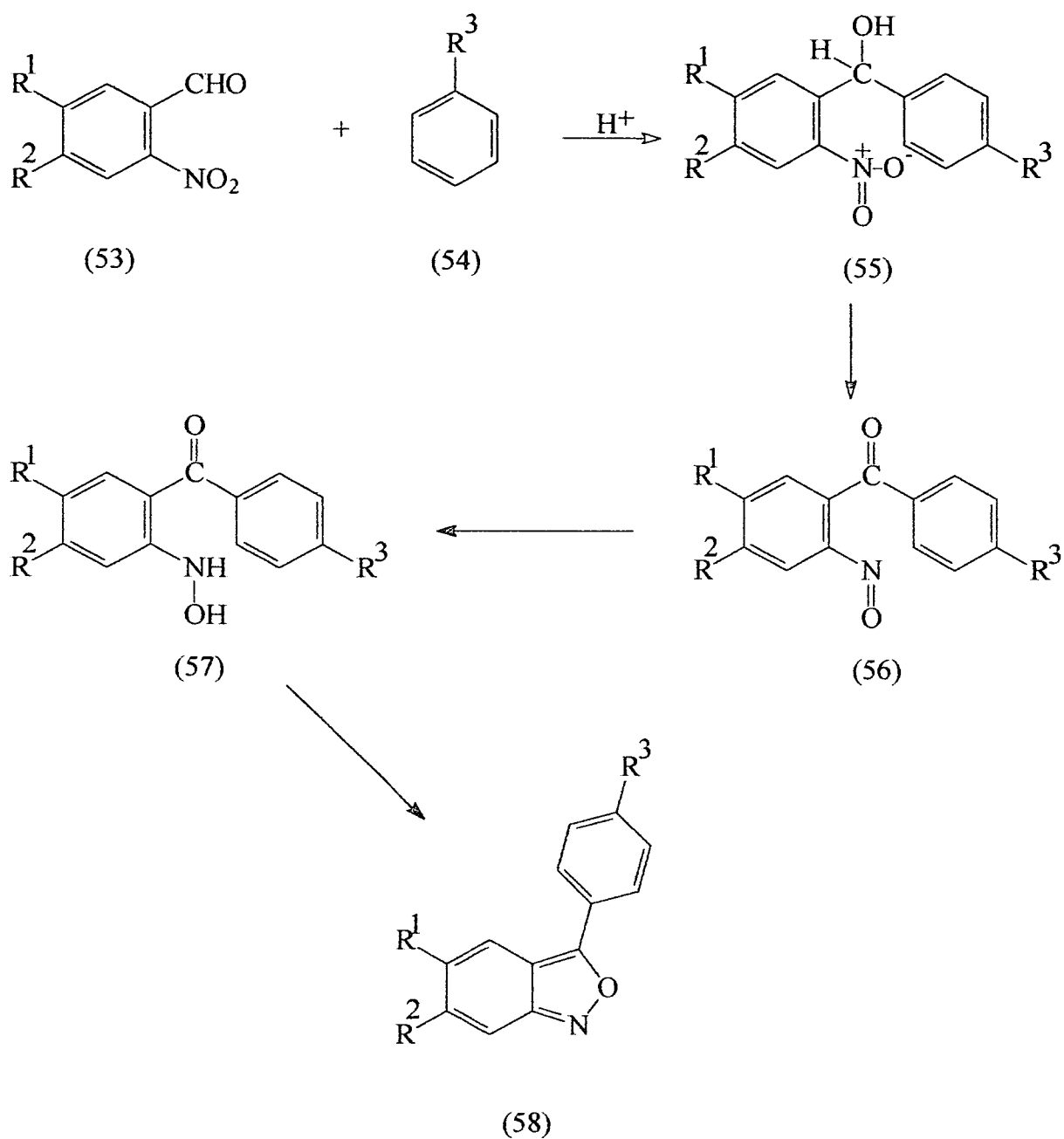
3.1 Formation of Five- membered Heterocycles

Formation of 2,1-benzisoxazoles (anthranils) provide some of the earliest examples of electrophilic nitro- group side- chain interactions in ortho- substituted nitrobenzene derivatives. For example (Scheme 8) 2,1-benzisoxazole-3- carboxaldehyde (52) was formed in moderate to low yield when 3-(2- nitrophenyl)oxirane-2-carboxylic acid (45) was heated with glacial acetic acid.³⁶ This transformation can be explained in terms of a mechanism [Scheme 8; (45)→→(48)] involving nucleophilic attack by the nitro- group on the protonated oxirane ring to afford, via the cyclic species (47), a nitroso intermediate (48). This can then lose carbon dioxide and undergo indirect internal oxidation- reduction to form the hydroxyamino-keto-aldehyde (51). Condensation between the hydroxyamino group



(i) AcOH, heat.

Scheme 8



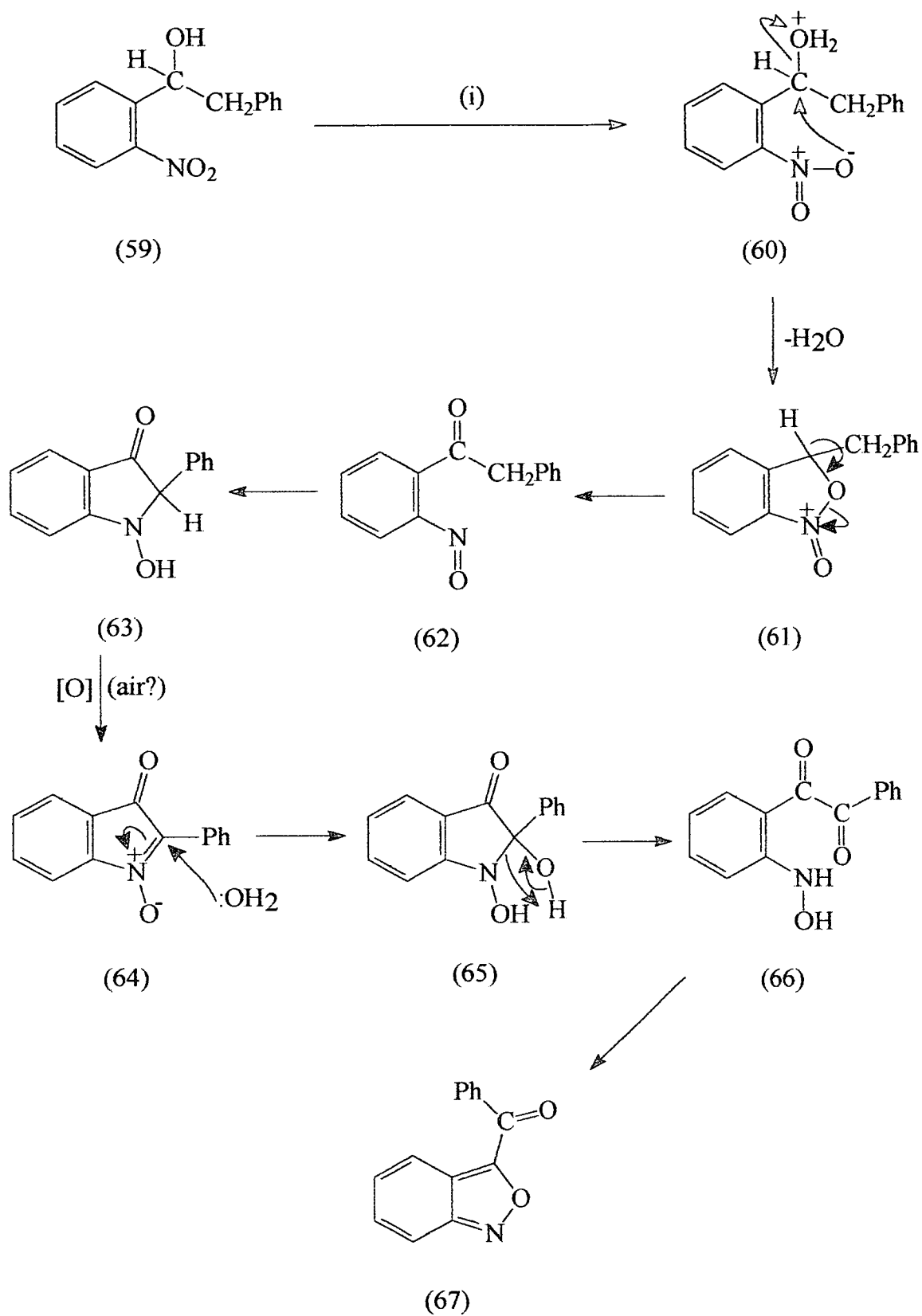
[R¹ = H, Cl; R² = H, NO₂; R³ = H, Me, Br, NMe₂, OH]

Scheme 9

and the ketonic carbonyl group in the latter then affords the 2,1-benzisoxazole carboxaldehyde (52).

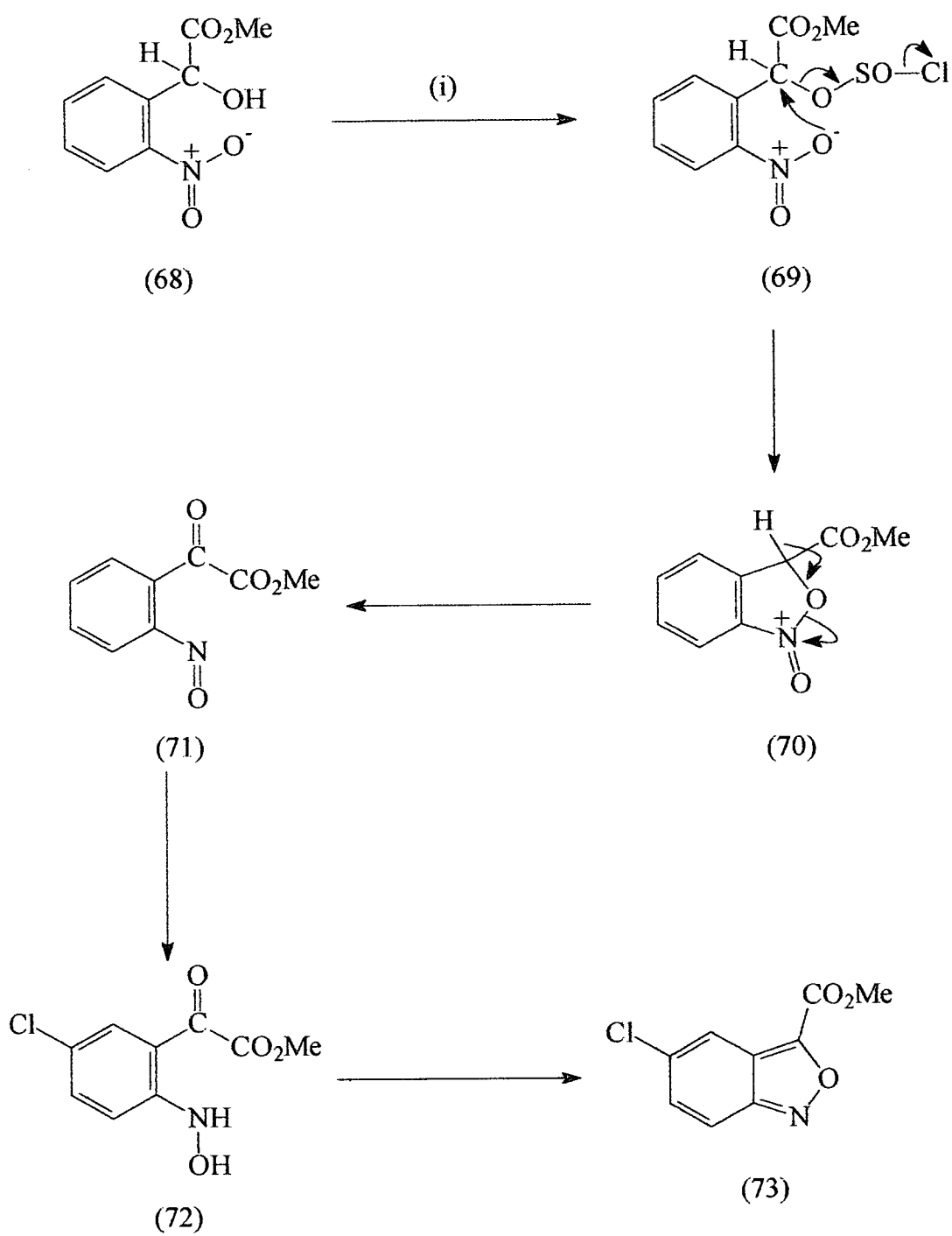
3-Aryl-2,1-benzisoxazoles [Scheme 9; (58)] are also the end products of the condensation of 2-nitrobenzaldehyde derivatives (53) with arenes, phenols, or arylamines (54) in the presence of a variety of acidic catalysts. Acids which catalyse such transformations include concentrated sulfuric acid,³⁷⁻⁴¹ hydrogen halides,^{42,43} and aqueous hydrochloric acid.^{44,45} The mechanism of such reactions (Scheme 9) is thought to involve the initial condensation of the aldehyde (53) with the benzene derivative (54) to form the benzhydrol intermediate (55). Nucleophilic attack [(55)→→(57)] by the nitro group in this intermediate on the electrophilic side-chain results in the formation of the nitroso intermediate (56). This intermediate (56) then undergoes reduction to a hydroxylamine derivative (57) which readily cyclises to afford the benzisoxazole derivative (58). The way in which the reduction step [(56)→(57)] occurs depends upon the acid catalyst used. In the case of sulfuric acid as catalyst, 2-nitrosobenzophenone (56) is reduced by unreacted benzhydrol (55) giving the hydroxylamine intermediate (57), and 2-nitrosobenzophenone which can often be isolated as a by-product.³⁷ In the case of hydrogen chloride, 2-nitrosobenzophenone (56) is reduced indirectly by reaction through nucleophilic substitution of the benzene ring by chloride ion giving the chlorinated hydroxylamine intermediate (57; $R^1=Cl$). This reduction therefore leads to the formation of chlorinated 2,1-benzisoxazoles (58; $R^1=Cl$). Non-chlorinated 2,1-benzisoxazoles (58; $R^1=H$) are produced when hydrogen bromide, or hydrogen chloride in the presence of quinol,⁴³ is utilised as the catalyst. In these cases reduction of the nitroso intermediate (56) by hydrogen bromide or quinol leads directly to the hydroxylamine derivative (57; $R^1=H$) and hence the 2,1-benzisoxazole (58; $R^1=H$) without the introduction of halogen.

A further example of the acid-catalysed conversion of an ortho-nitroaromatic derivative into a 2,1-benzisoxazole derivative involves the conversion (Scheme 10) of 1-(2-nitrophenyl)-2-phenylethanol (59) into the 2,1-benzisoxazole derivative (67) catalysed by toluene-4-sulphonic acid.⁴⁶ The proposed mechanism for this transformation involves initial nucleophilic attack by the nitro-group on the



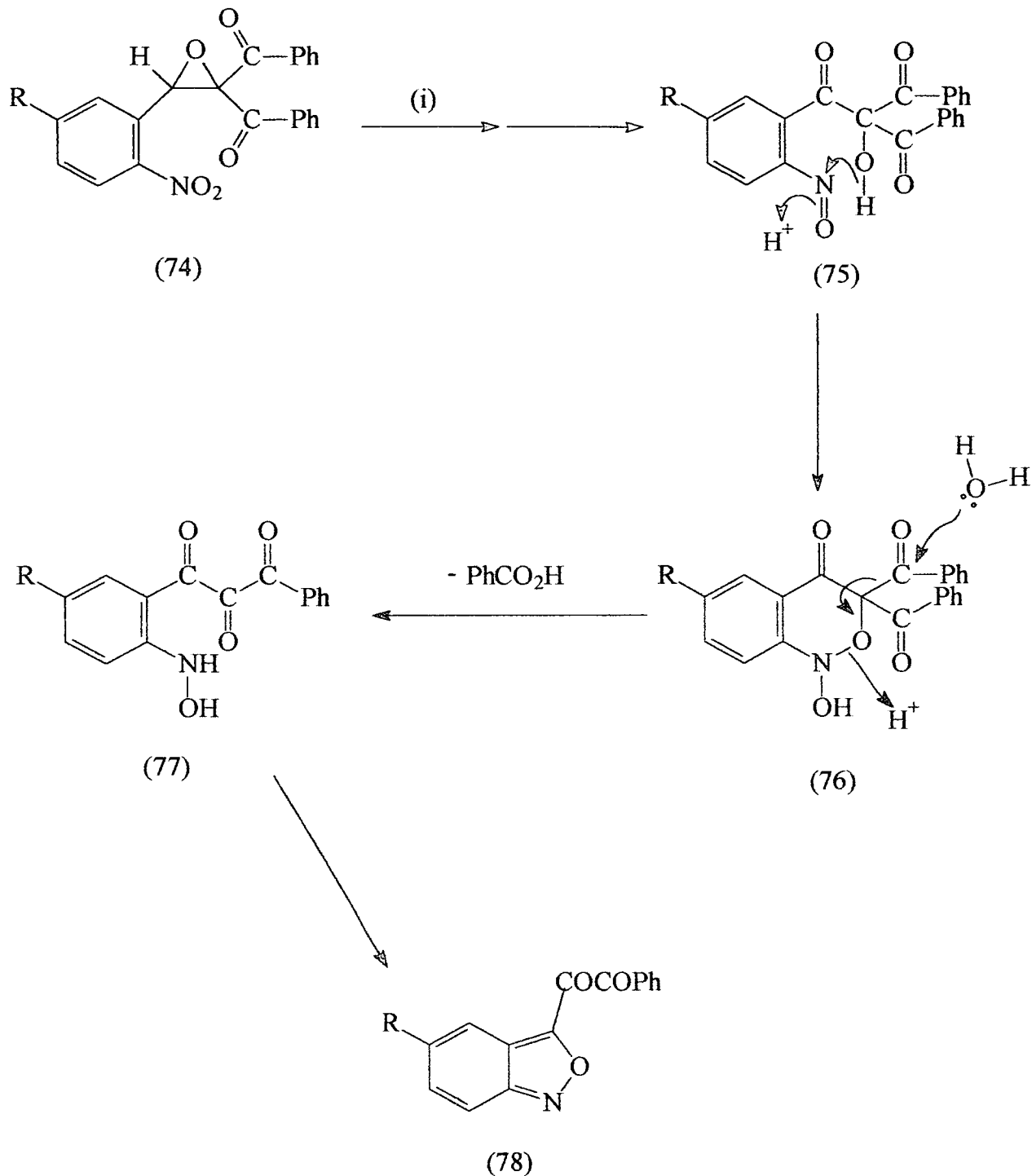
(i) toluene-4-sulphonic acid, toluene, reflux.

Scheme 10



(i) SOCl_2 , reflux.

Scheme 11



R
 a; H
 b; Cl
 c; Br

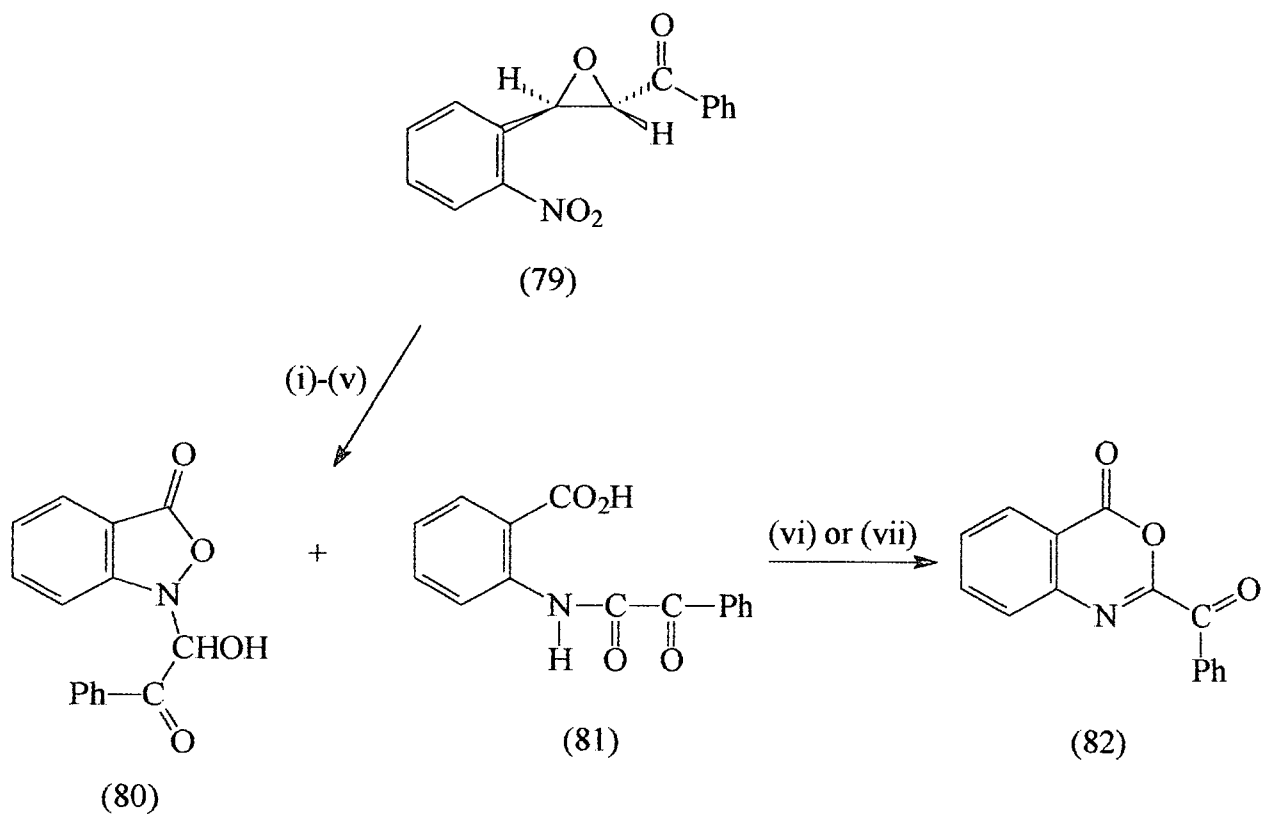
(i) $\text{H}_3\text{PO}_4\text{-P}_2\text{O}_5$, heat.

Scheme 12

protonated side- chain leading to the nitroso-ketone derivative (62) via the formation and ring-opening of the cyclic intermediate (61). The nitroso-ketone (62) is then believed to cyclise to 2-phenylisatogen (64) via the formation and possible aerial oxidation of the N-hydroxy-3-oxoindole derivative (63). 2-Phenylisatogen (64) is known⁴⁷ to undergo transformation into 3-benzoyl-2,1-benzisoxazole (67) under acidic conditions via the presumed intermediates (65) and (66).

Heating (Scheme 11) methyl 2-nitromandelate (68) under reflux with a four- fold excess of thionyl chloride converted it in excellent yield into the corresponding 2,1-benzisoxazole derivative (73).⁴⁸ The mechanism of this reaction can be viewed as involving nucleophilic attack by the nitro group on the ortho- side- chain after activation of the hydroxyl group by thionyl chloride. Loss of sulfur dioxide and hydrogen chloride would then lead, via a cyclic intermediate, to an ortho- nitroso keto-ester [(68)→(69)→(70)→(71)]. Cyclisation of the nitroso- keto-ester (71) via the formation and ring- closure of the chlorinated hydroxylamine derivative (72) then accounts for the formation of the chlorinated 2,1-benzisoxazole ester product (73). In comparison, the conversion of methyl 5-chloro-2-nitromandelate into methyl 5,7-dichloro-2,1-benzisoxazole-3-carboxylate required heating under reflux with a seventy- fold excess of thionyl chloride. The difference in reactivity between methyl 2-nitromandelate (68) and its 5-chloro derivative may be due in the latter case to increased steric hindrance to the introduction of chloride ion at the 7- position in the formation of the hydroxylamine intermediate.

The acid- catalysed cyclisation reactions of 2,2-dibenzoyl-3-(2-nitrophenyl)oxiranes with polyphosphoric acid also result in 2,1-benzisoxazole formation through electrophilic nitro group side- chain interaction. Thus, treating (Scheme 12) the parent oxirane (74a) with polyphosphoric acid at 80°C gave the corresponding 2,1-benzisoxazole derivative (78a).⁴⁹ Similar treatment of the chlorinated and brominated oxirane analogous (74b and c) also resulted in cyclisation to the corresponding 2,1-benzisoxazole derivatives (78b and c). However, the presence of the halogen substituent para to the nitro group had a retarding effect on 2,1-benzisoxazole formation. It was found that the reaction times were significantly longer⁴⁹ for the halogenated substrates (74b and c) compared with the parent oxirane (74a). The



- (i) $\text{H}_3\text{PO}_4\text{-P}_2\text{O}_5$, room temp. or heat.
- (ii) SnCl_4 , benzene, room temp.
- (iii) $\text{BF}_3\cdot\text{Et}_2\text{O}$, benzene, reflux.
- (iv) HCO_2H , heat.
- (v) SnCl_4 , HCl(g) , ether, 0°C .
- (vi) Ac_2O , reflux.
- (vii) Ac_2O , NaOAc , heat.

Scheme 13

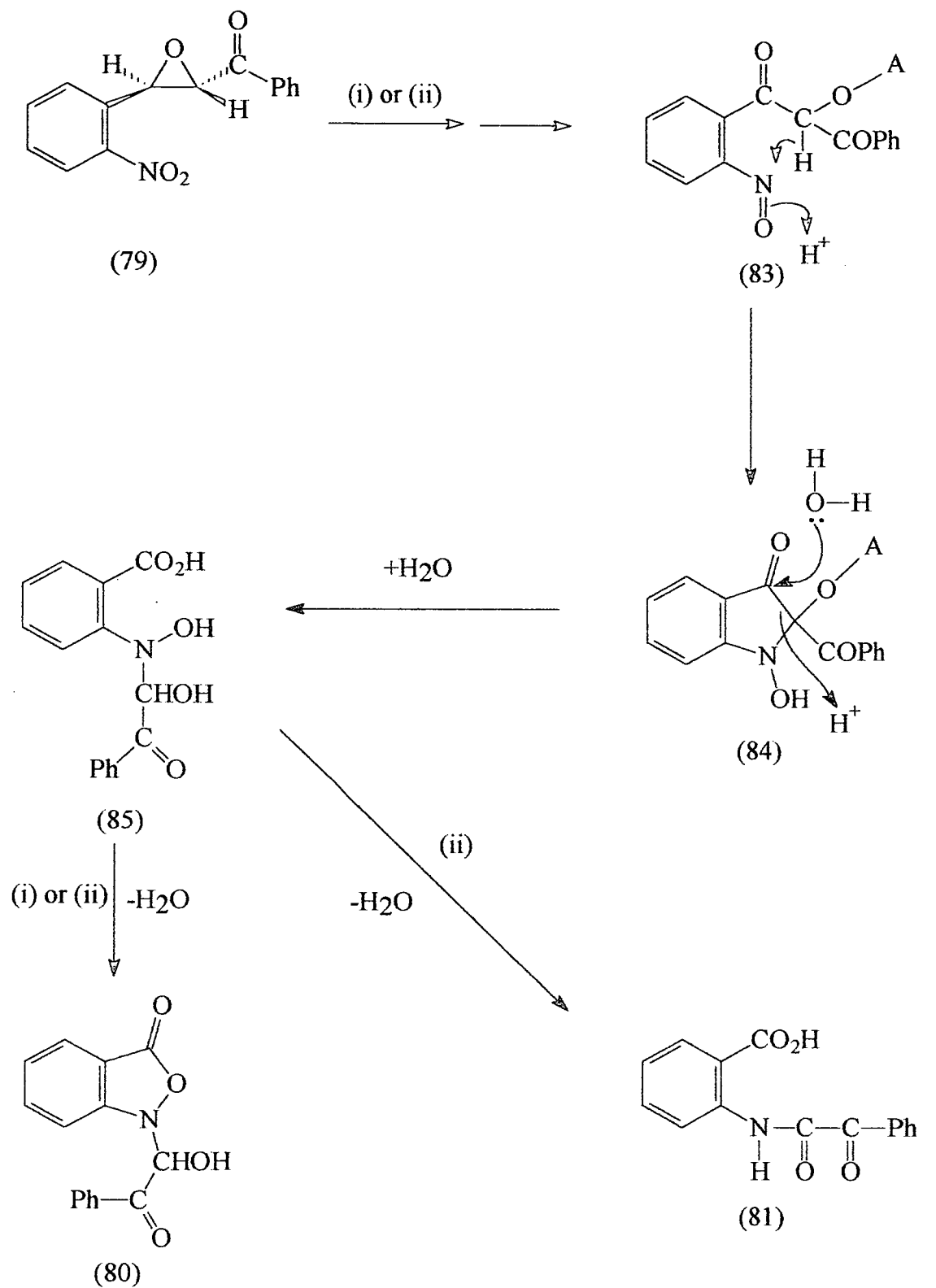
halogen atom in the halogenated substrates (74b and c) may be withdrawing electron density away from the nitro group thus reducing its capacity for nucleophilic attack on the electron- deficient side- chain.

Once again the acid- catalysed conversion of the oxirane derivatives (74) into the 2,1-benzisoxazole products (78) may be viewed (Scheme 12) as involving initial formation of the ortho- nitrosobenzene intermediates (75). These can be transformed into ortho- hydroxyamino triketone derivatives (77) through the intermediacy and deacylative ring- opening of initially formed cyclic intermediates (76). Ring- closure of the hydroxyamino triketones (77) then accounts for the formation of the 2,1-benzisoxazole products (78).

In contrast to the acid- catalysed transformation of the dibenzoyloxirane (74a) into the 2,1-benzisoxazole derivative (78a), treatment (Scheme 13) of *trans* 2-benzoyl-3-(2-nitrophenyl)oxirane (79) with polyphosphoric acid at room temperature or 80°C gave the isomeric 2-N-(1,2-dioxo-2-phenyl)ethylaminobenzoic acid (81) in moderate yield.⁴⁹ Heating this 2-aminobenzoic acid derivative (81) with acetic anhydride under reflux gave the 3,1-benzoxazine derivative (82) in good yield. Similarly the oxirane derivative (79) was converted in low yield into the 2-aminobenzoic acid derivative (81) by heating in formic acid.⁵⁰

Lewis acids have also been found to catalyse electrophilic cyclisation reactions of ortho- substituted nitroaromatic derivatives. Treating (Scheme 13) the *trans* 2-nitrophenyloxirane derivative (79) with stannic chloride in benzene at room temperature gave a high yield of the 3-oxo-2,1-benzisoxazole derivative (80). The structure of this product was confirmed by its unambiguous synthesis by condensation of 1,3-dihydro-3-oxo-2,1-benzisoxazole with 2-oxophenylacetaldehyde.⁵⁰

In comparison with the stannic chloride catalysed reaction, boron trifluoride etherate converted (Scheme 13) the 2-nitrophenyloxirane derivative (79) in benzene into a mixture of the 3-oxo-2,1-benzisoxazole derivative (80) and the



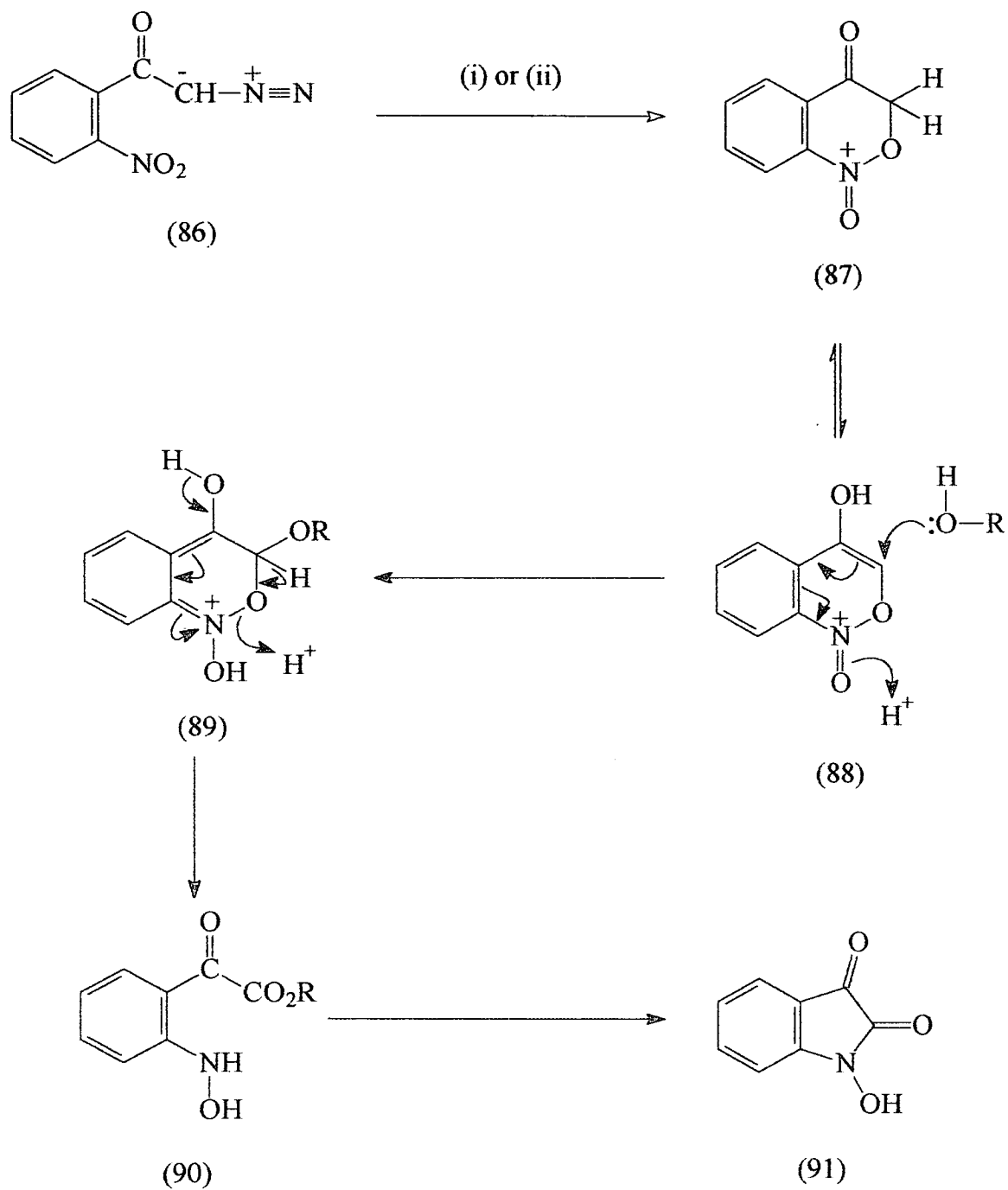
- (i) SnCl_4 , benzene, room temp.
 (ii) $\text{BF}_3 \cdot \text{Et}_2\text{O}$, benzene, reflux.

Scheme 14

2-aminobenzoic acid derivative (81). Moderate yields were obtained for each of these products.⁵⁰ The structure of the 2-aminobenzoic acid derivative (81) was confirmed by its unambiguous synthesis by reaction of 2-aminobenzoic acid with 2-oxophenylethanoyl chloride.⁵⁰ Also (Scheme 13), the oxirane derivative (79) was transformed by treatment with stannic chloride in ether in the presence of hydrogen chloride into the 2-aminobenzoic acid derivative (81) in excellent yield.⁵⁰ Moreover, the 3-oxo-2,1-benzisoxazole derivative (80) is readily converted into the 2-aminobenzoic acid derivative (81) by treatment with cold aqueous sodium hydroxide solution or concentrated sulfuric acid. The 3-oxo-2,1-benzisoxazole derivative (80) was also transformed (Scheme 13) in good yield into 2-benzoyl-3-oxo-4H-3,1-benzoxazine (82) by heating with sodium acetate in acetic anhydride.⁵⁰

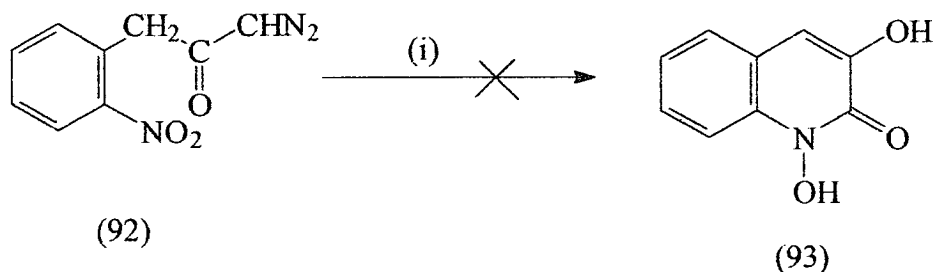
The proposed mechanism (Scheme 14) for the formation of the 3-oxo-2,1-benzisoxazole derivative (80) and the 2-aminobenzoic acid derivative (81) involves once again the initial creation of an ortho- nitroso intermediate (83) through nucleophilic participation of the nitro- group with the ortho side- chain [(79)→→(83)]. Subsequent cyclisation of the ortho- nitroso intermediate (83) affords a cyclic N-hydroxy species (84), hydrolytic ring- opening of which affords the 2-hydroxyaminobenzoic acid derivative (85). The latter can then undergo cyclodehydration to the 1,3-dihydro-3-oxo-2,1-benzisoxazole derivative (80) or side-chain dehydration to afford the 2-aminobenzoic acid derivative (81).

Glacial acetic acid as well as sulfuric acid have been shown to catalyse the cyclisation (Scheme 15) of 2-nitrobenzoyldiazomethane (86) into N-hydroxyisatin (91).⁵¹ Initial studies⁵² on the mechanism of this unusual transformation suggested that reaction occurred through a nitroso- aldehyde intermediate. However this pathway was rejected⁵³ since (Scheme 16) the homologous 1-diazo-3-



(i) AcOH, heat.
(ii) H₂SO₄, H₂O, heat.

Scheme 15

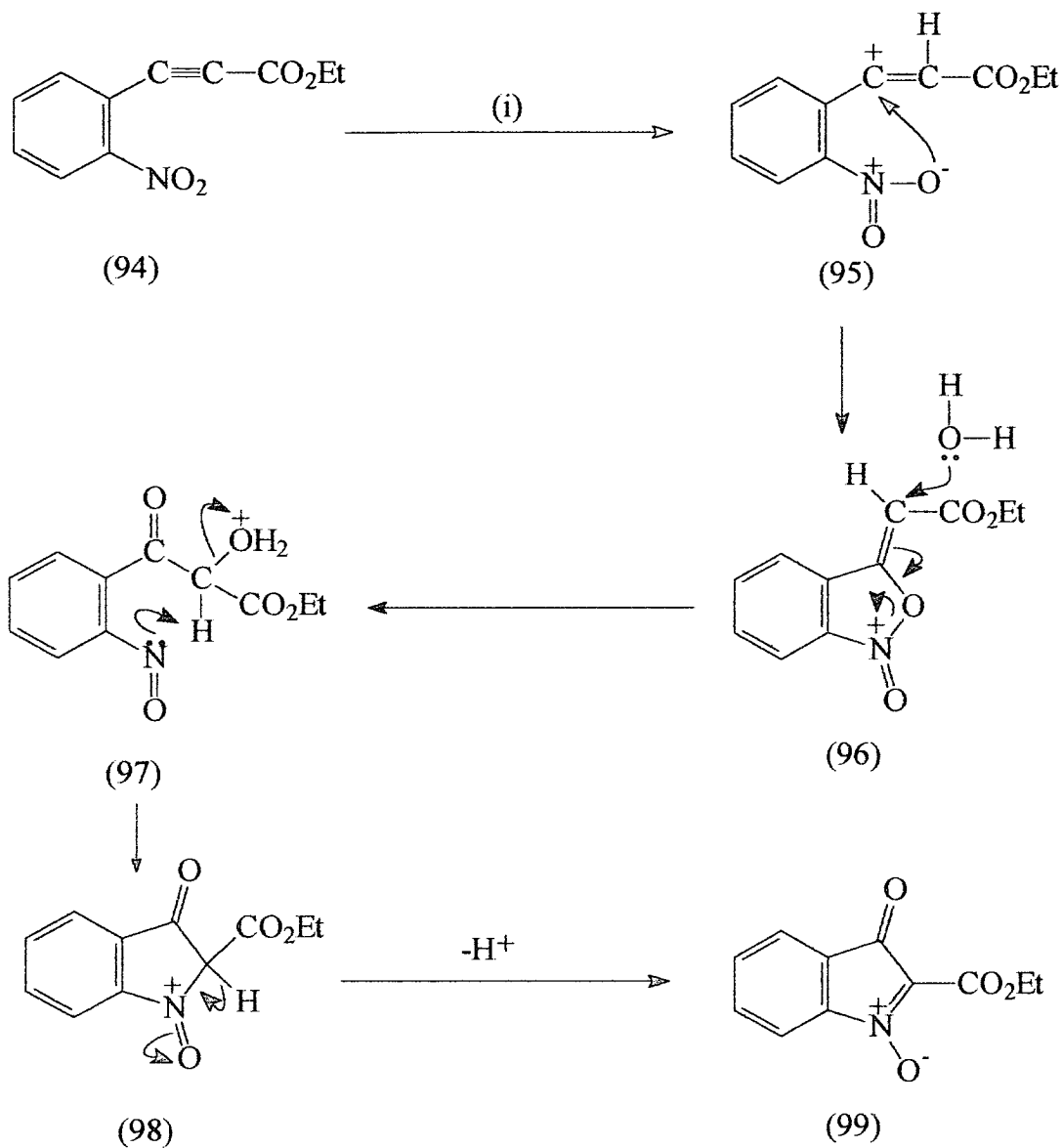


(i) AcOH, heat.

Scheme 16

(2-nitrophenyl)propanone (92) failed to undergo analogous acid- catalysed cyclisation to the N-hydroxy-2-oxoquinoline derivative (93). ^{13}C labelling⁵³ also established that a Wolff- type rearrangement was not involved in the reaction [(86)→(91)]. The currently proposed mechanism (Scheme 15) for this reaction involves nucleophilic attack by the negatively charged oxygen atom of the nitro-group on the electrophilic ortho side- chain with subsequent loss of nitrogen to form a cyclic intermediate [(86)→(87)]. Acid- catalysed enolisation of this intermediate [(87)→(88)] is then followed by reaction with acetate (in glacial acetic acid) or water (in dilute sulfuric acid) to afford the quinonoid- like intermediate (89). Ring opening of this intermediate gives the ortho- hydroxyaminophenyl keto acid (90a) [or the mixed anhydride (90b) if glacial acetic acid was utilised]. The latter then undergoes spontaneous cyclisation to form N-hydroxyisatin (91).

It has also been shown (Scheme 17) that treating ethyl 2-nitrophenyl propiolate (94) with concentrated sulfuric acid gives ethyl isatogen-2-carboxylate (99) in good yield.^{54,55} The proposed mechanism (Scheme 17) for this transformation involves the direct interaction of the nitro group with the protonated acetylenic side- chain to give a cyclic intermediate (96) convertible by subsequent hydrolytic ring- opening to an ortho nitroso species (97). Cyclisation of the latter then affords the isatogen derivative (99) via proton loss and electron reorganisation of the initial cyclic intermediate (98).



(i) H_2SO_4 (conc.), room temp.

Scheme 17

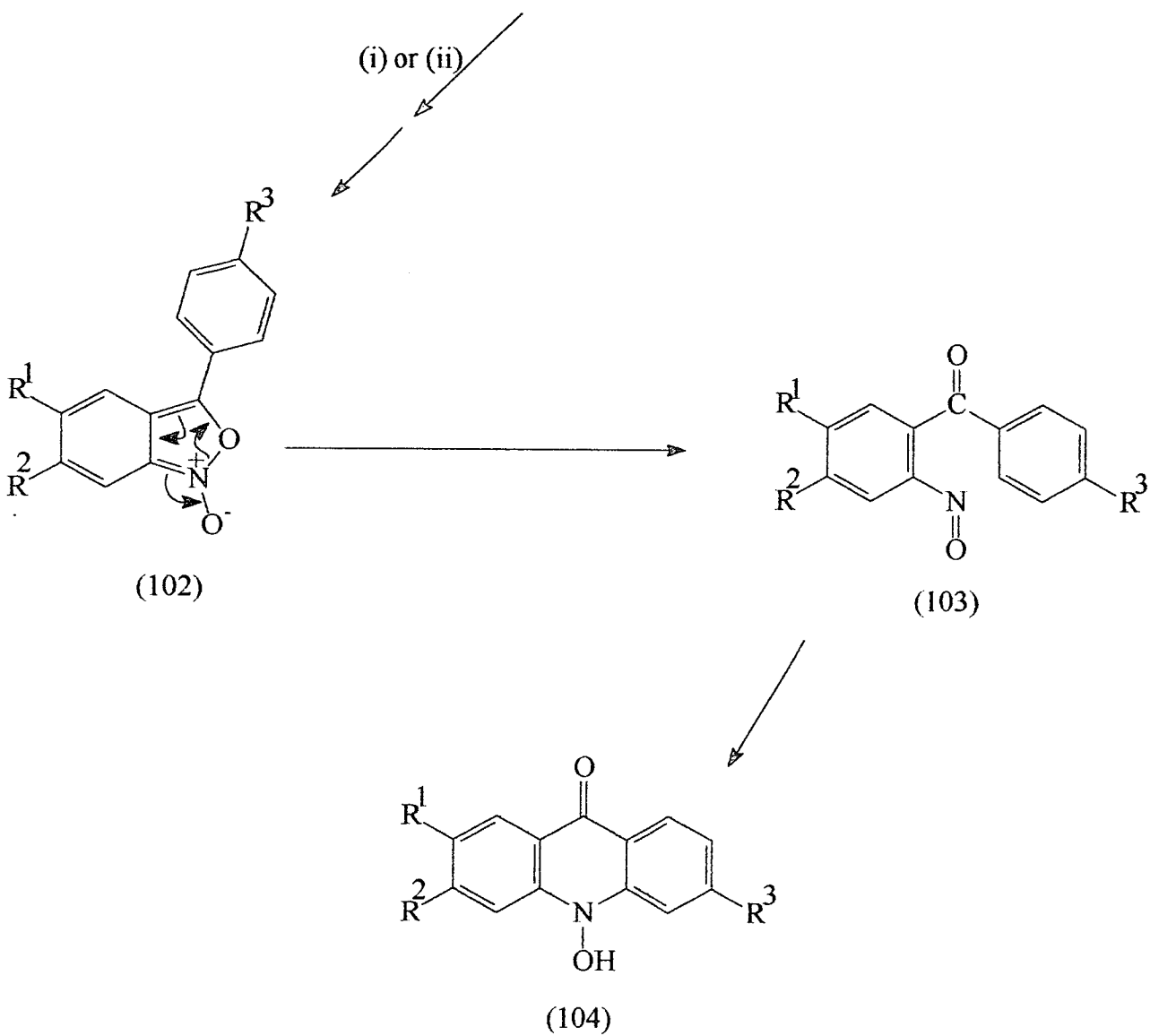
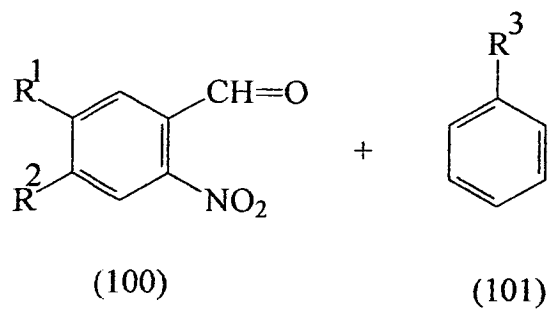
3.2 Formation of Six- membered Heterocycles

Acid- catalysed electrophilic cyclisation reactions of ortho- substituted nitroaromatic compounds also lead to six- membered heterocycles. In such cyclisations unlike those leading to five- membered heterocycles N-oxygenated compounds are the predominant products.

The condensation (Scheme 18) of 2-nitrobenzaldehydes (100) with aromatic hydrocarbons (101) in cold concentrated sulfuric acid gives moderate yields of the corresponding 9-oxoacridines and their N-hydroxy derivatives (104).⁵⁶⁻⁶⁰ Improved yields of these acridine derivatives (104) resulted when the condensation of 2-nitrobenzaldehydes (100) with aromatic hydrocarbons (101) was carried out in concentrated sulfuric acid in the presence of sodium nitrite.⁶¹ 9-Oxoacridine formation has been postulated (Scheme 18) to involve the initial condensation of the aldehyde (100) with the benzene derivative (101) as shown before in Scheme 9 to give the corresponding 2,1-benzisoxazole derivative (102). This intermediate undergoes ring- opening thought to be catalysed by sodium nitrite,^{57,61-64} to afford an ortho- nitroso- ketone intermediate (103) which then cyclises to the N-hydroxy-9-oxoacridine (104).

Polyphosphoric acid has been utilised as a catalyst in the synthesis of N-hydroxy 9-oxoacridines and benzacridines. Thus treating⁶⁵ (Scheme 19) a mixture of 2-nitrobenzaldehyde (105) and naphthalene (106) with polyphosphoric acid afforded a mixture of the N-hydroxybenzacridine (107) and the 2,1-benzisoxazole derivative (108).

Acid- catalysed cyclisation reactions of ortho- substituted nitroaromatic derivatives provides an excellent route to otherwise inaccessible N-oxygenated quinolinone derivatives (Scheme 20). 2-Nitrobenzaldehyde (105) reacts with active methylene compounds, such as pentane-2,4-dione, in the presence of hydrogen chloride or hydrogen bromide to form N-hydroxy-4-oxoquinolines (113) and (114).⁶⁶ The mechanism of such reactions is thought to involve the initial condensation of the aldehyde (105) with the active methylene compound to give the 2-nitrobenzylidene derivative (109). By analogy with related processes discussed before, nucleophilic



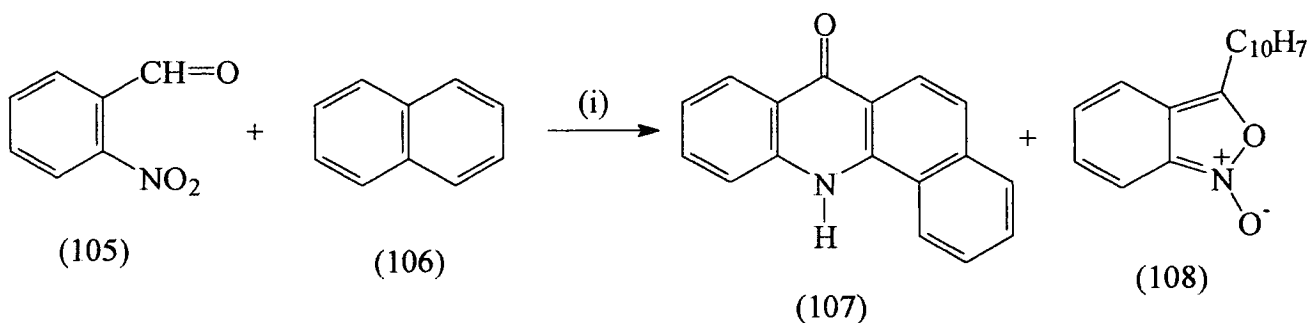
[R¹ = H, Cl; R² = H, Cl, NO₂; R³ = H, Me, Br, I, Cl]

(i) H₂SO₄ (conc.), 0°C.

(ii) NaNO₂, H₂SO₄ (conc.), 0°C.

Scheme 18

attack by the nitro- group in the benzylidene derivative (109) on the benzylidene side- chain affords the nitroso- ketone intermediate (111) which may suffer reduction



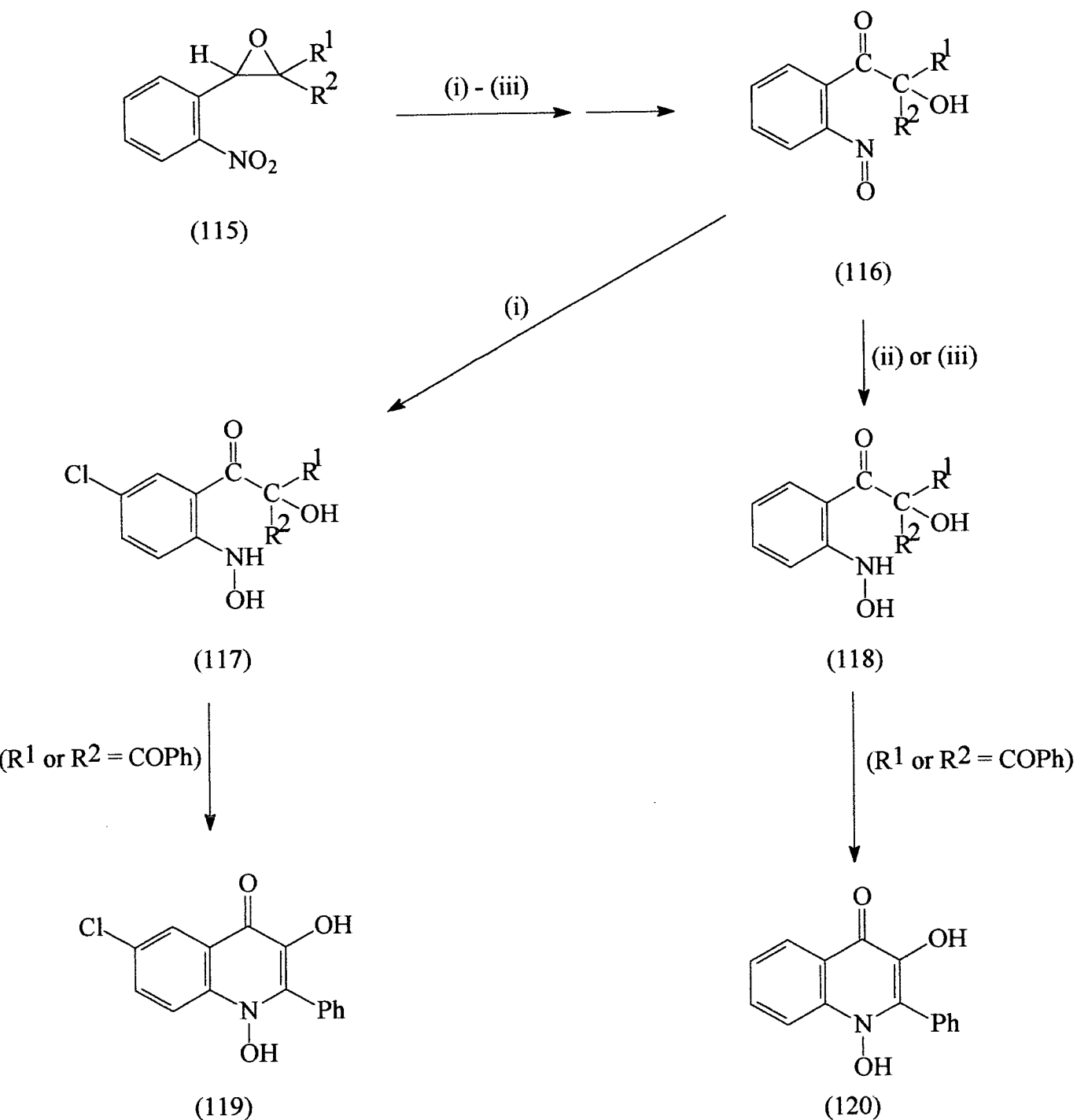
(i) P₂O₅-H₃PO₄, heat.

Scheme 19

to a hydroxyamino derivative in two ways depending on the acid catalyst used. In the presence of hydrogen chloride the nitroso- ketone (111) is converted into the halogenated phenylhydroxylamine intermediate (110). This intermediate then undergoes cyclisation to afford a halogenated N-hydroxy-4-oxoquinoline derivative (113). Direct reduction of the nitroso intermediate (111) using hydrogen bromide or hydrogen chloride with hydroquinone gives an unhalogenated hydroxylamine intermediate (112) which subsequently cyclises to give an unhalogenated N-hydroxy-4-oxoquinoline derivative (114).⁴³

In a very similar process⁶⁷ (Scheme 21), 2-nitrophenyloxiranes (115) are converted in ether in the presence of hydrogen chloride into the chlorinated N-hydroxy-4-oxoquinoline (119). Changing the catalyst in this reaction to hydrogen bromide, or hydrogen chloride in the presence of hydroquinone, results in the formation of the non- halogenated N-hydroxy-4-oxoquinoline (120).

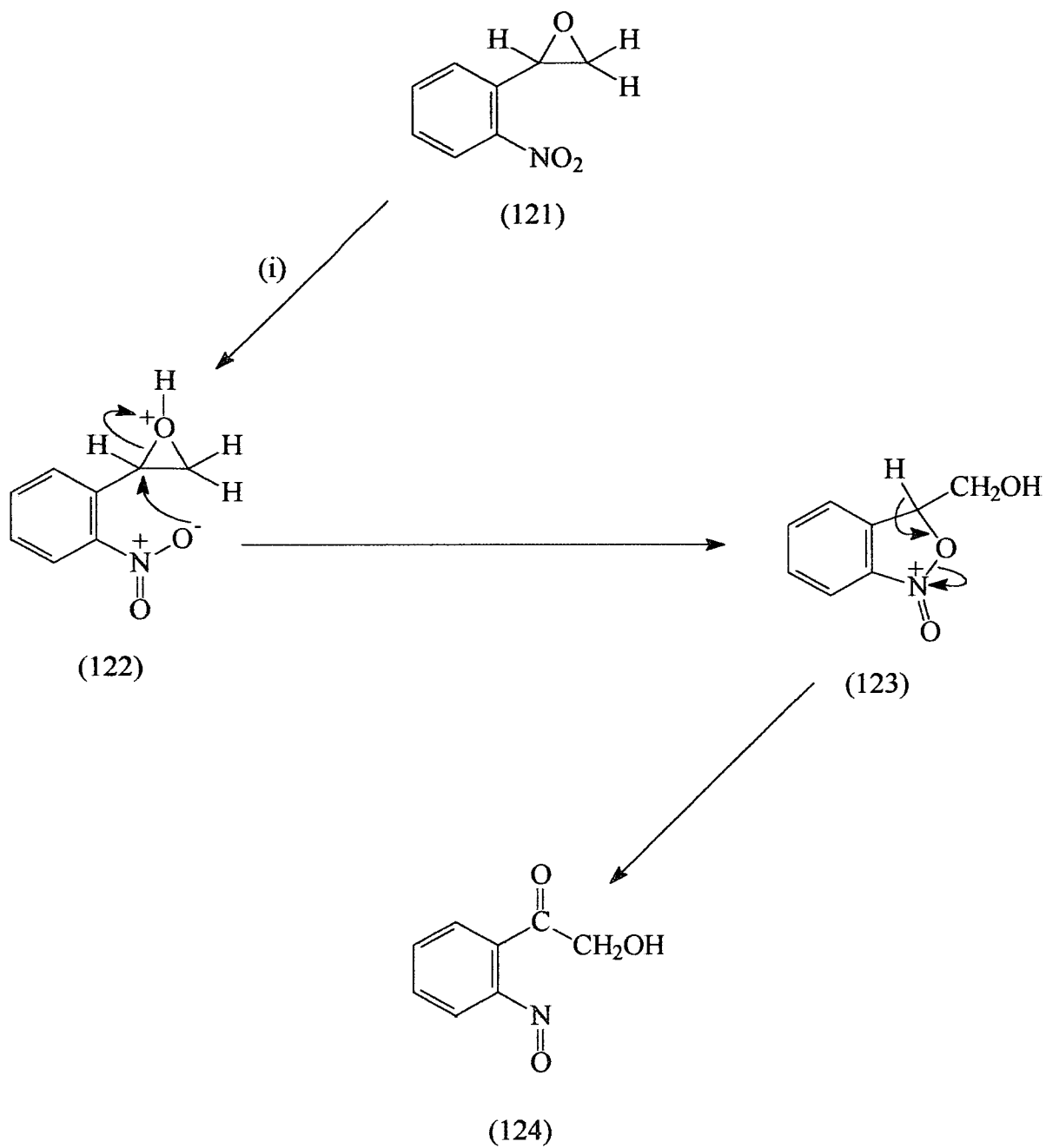
Both the diacyl oxirane derivatives (115; R¹=MeCO or PhCO, R²=PhCO) and the *cis* oxirane derivative (115; R¹=H; R²=PhCO) are converted in ether in the presence of hydrogen chloride into the N-hydroxy-4-oxoquinoline (119) in high yields. In



[$R^1 = \text{H, MeCO or PhCO}$; $R^2 = \text{MeCO or PhCO}$]

- (i) HCl(g) , ether, 0°C .
- (ii) HBr(g) , ether, 0°C .
- (iii) HCl(g) , hydroquinone, ether, 0°C .

Scheme 21



(i) HCO₂H, heat.

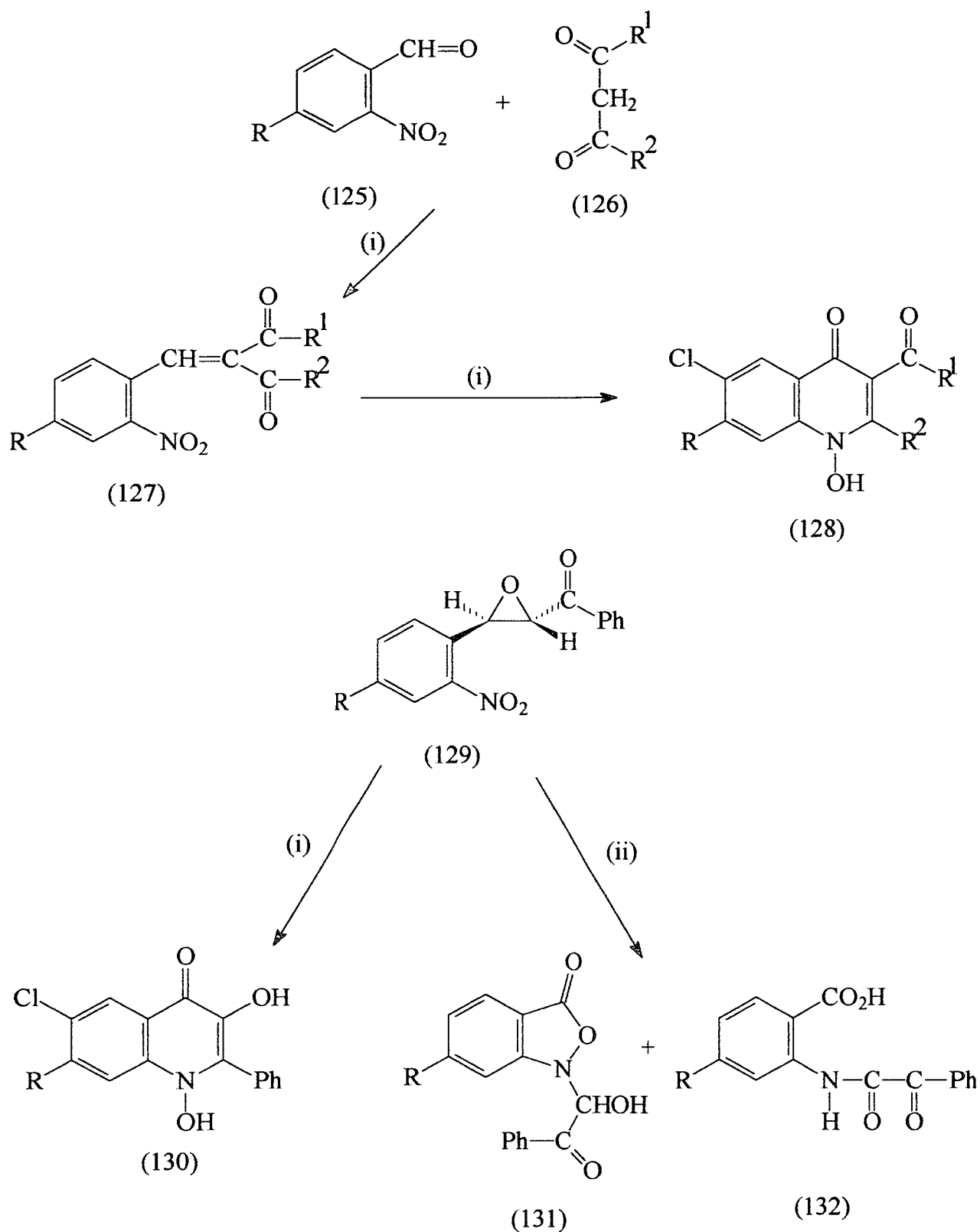
Scheme 22

contrast, a poor yield of the N-hydroxy-4-oxoquinoline (119) was isolated when the *trans* oxirane derivative (115; $R^1=\text{COPh}$, $R^2=\text{H}$) was subjected to the same reaction conditions.^{68,69} The high isolated yields of the N-hydroxy-4-oxoquinoline (119) in the former examples is thought to be due to the steric effect of the *cis* acyl group in the oxirane derivatives (115; $R^2=\text{PhCO}$ or MeCO).⁶⁹ The *cis* acyl group is thought to cause the nitrophenyl group in the oxirane derivative to twist into a more favourable position for reaction with the ortho side-chain. Again the proposed mechanism for this reaction is thought to involve nucleophilic participation of the nitro-group with the ortho side-chain in the oxirane derivative [(115)→→(116)] which leads to the initial creation of an ortho-nitroso intermediate (116). This intermediate may then be reduced in either of two ways as previously discussed (See Scheme 20) to afford the hydroxyamino intermediate (117) or (118). Intramolecular cyclisation of the intermediates (117) and (118) results in the formation of the respective N-hydroxy-4-oxoquinolines (119) and (120).

Evidence for the reaction mechanisms of the acyl-2-nitrophenyloxirane cyclisations shown in Scheme 21 comes from the related reaction (Scheme 22) of 2-nitrophenyloxirane (121) with formic acid to give 2-nitrosobenzoylmethanol (124).⁷⁰ This result supports a reaction pathway for the initial stage [Scheme 21; (115)→(116)] of N-hydroxy-4-oxoquinoline formation, of intramolecular nucleophilic attack by the nitro-group on the protonated oxirane ring to form a cyclic intermediate which subsequently undergoes ring opening to produce the key ortho-nitrosobenzene intermediate (124) [See Scheme 22; (121)→(122)→(123)→(124)].

CHAPTER 2

STUDIES ON THE SCOPE OF THE ACID CATALYSED
CYCLISATION REACTIONS OF 2-NITROBENZENE
DERIVATIVES TO 1-HYDROXY 4-QUINOLONE DERIVATIVES
AND RELATED PROCESSES



[R=EWG or EDG]
 [R¹, R²= alkyl or aryl]

(i) acid catalyst.
 (ii) Lewis acid catalyst.

Scheme 23

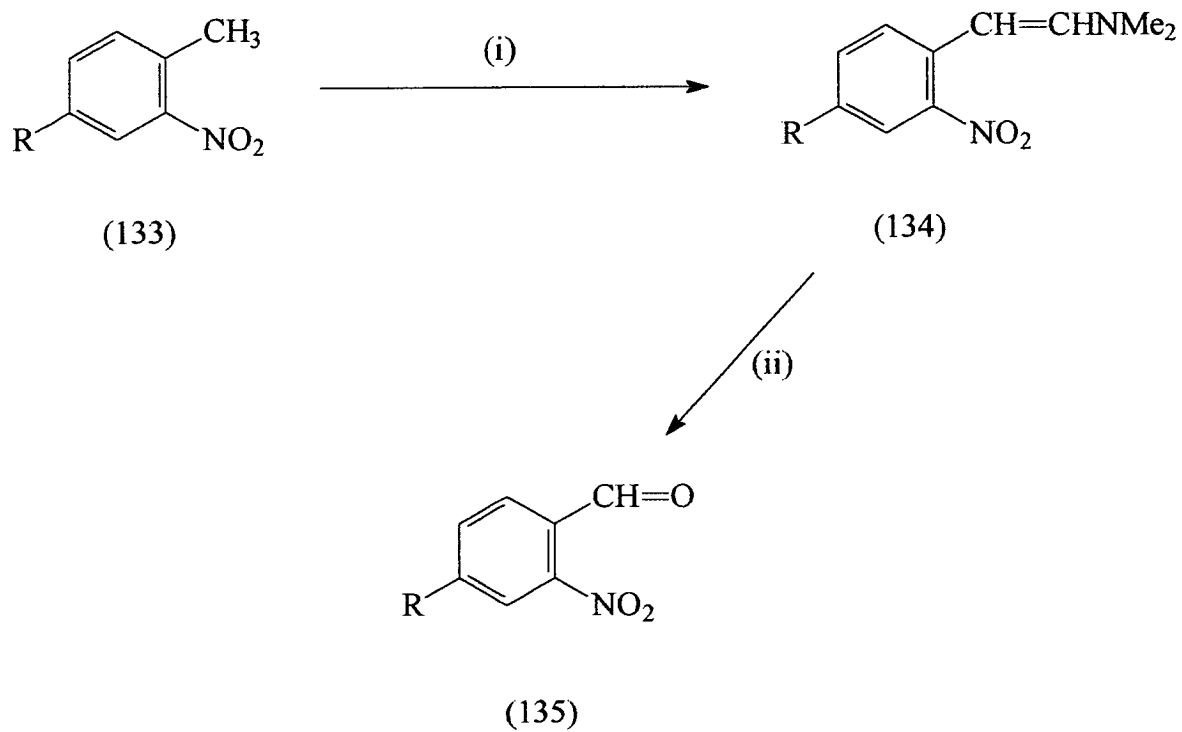
STUDIES ON THE SCOPE OF THE ACID CATALYSED CYCLISATION
REACTIONS OF 2-NITROBENZENE DERIVATIVES TO 1-HYDROXY 4-
QUINOLONE DERIVATIVES AND RELATED PROCESSES

1. INTRODUCTION

The present studies were undertaken to investigate the scope of, and substituent effects in, the acid catalysed cyclisation reactions of 2-nitrobenzene derivatives to 1-hydroxy 4-quinolone derivatives. The discussion will centre around three areas. Firstly (Scheme 23) the acid catalysed cyclisation of the 2-nitrobenzylidene derivatives (127) to the 1-hydroxy 4-quinolones (128). The former derivatives are proposed as intermediates and are formed in situ from the acid catalysed condensation of the 2-nitrobenzaldehyde (125) with the diacylmethane derivative (126). Extension of previous work (see Chapter 1, section 3.2, page 18 and Scheme 20) involved investigating substituent effects para to the side-chain in the nitrobenzylidene derivatives (127) with regard to their acid catalysed cyclisation to the N-hydroxyquinolinones (128). Secondly studies were carried out on the scope of, and substituent effects in, the acid catalysed cyclisation of the nitrophenyloxirane derivatives (129) to the novel 1,3-dihydroxyquinolinones (130) (see Chapter 1, section 3.2, page 19 and Scheme 21). Thirdly investigations were carried out on the substituent effects in the Lewis acid catalysed reactions of the nitrophenyloxirane derivatives (129) to give the 2,1-benzisoxazolone and the related 2-aminobenzoic acid derivatives (131) and (132).

2. STUDIES ON THE SCOPE OF THE ACID- CATALYSED CYCLISATION
REACTIONS OF 2-NITROBENZYLIDENE DERIVATIVES TO 1-HYDROXY
4-QUINOLONES

Initially (Scheme 23) investigations under this heading centred on the 4-methyl-2-nitrobenzylidene derivatives (127; R=Me). Studies were carried out on the effects of a methyl group (an electron donating group) para to the side-chain in the 2-nitrobenzylidene derivatives (127; R=Me) when these derivatives were treated with hydrogen chloride. It was thought the methyl substituent in the nitrobenzylidene

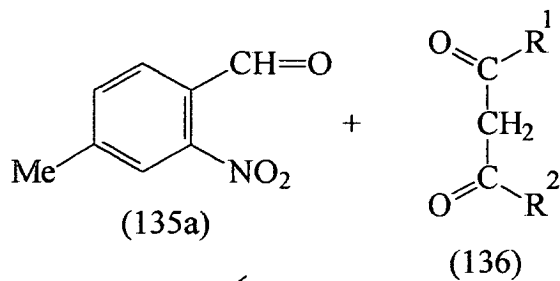


R
a; Me
b; Cl
c; NO₂

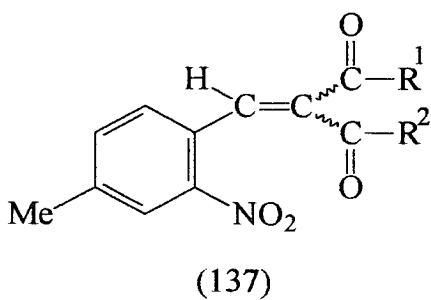
(i) Me₂NCH(OMe)₂, DMF, reflux.

(ii) NaIO₄, THF, H₂O, room temp.

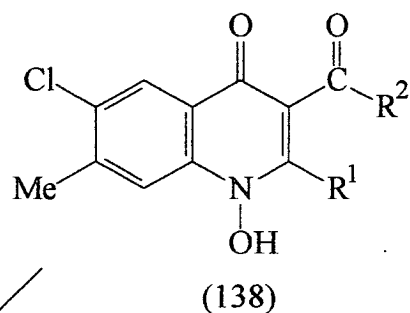
Scheme 24



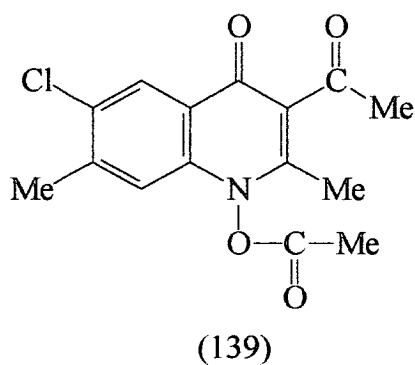
(i)-(iii)



(i)



(iv) ($R^1=R^2=Me$)



	R^1	R^2
a;	Me	Me
b;	Me	Ph
c;	Ph	Ph
d;	Me	OEt
e;	Ph	OEt

- (i) $HCl_{(g)}$, ether or DME, $0^\circ C$.
 (ii) piperidine, DME or AcOH, room temp.
 (iii) NaOEt, EtOH, room temp.
 (iv) Ac_2O , $100^\circ C$.

Scheme 25

derivative (127; R=Me) may reduce the electrophilicity of the side- chain by donating electrons into the benzene ring. As a consequence the nucleophilic nitro group ortho to the side- chain in the nitrobenzylidene derivative (127; R=Me) may not react as readily with the side- chain in the presence of hydrogen chloride to ultimately give the N-hydroxyquinolinone derivative (128; R=Me). The general strategy for the preparation of the 4-methyl-2-nitrobenzylidene derivatives (127; R=Me) required for subsequent acid catalysed cyclisation to the N-hydroxyquinolinone derivatives (128; R=Me) involved the initial synthesis (Scheme 24) of 4-methyl-2-nitrobenzaldehyde (135a). The synthesis of the known⁷¹ nitrobenzaldehyde (135a) was readily accomplished by the method outlined in Scheme 24. Heating 2-nitro-p-xylene (133a) with N,N-dimethylformamide dimethyl acetal in dimethylformamide under reflux gave a quantitative yield of the enamine derivative (134a). This enamine derivative (134a) was smoothly converted into the 2-nitrobenzaldehyde (135a) in high yield in the presence of sodium periodate in aqueous tetrahydrofuran.

Previous work (see Chapter 1, section 3.2, page 18 and Scheme 20) had shown how 2-nitrobenzaldehyde reacted with pentane-2,4-dione to give the corresponding N-hydroxyquinolinone derivative in high yield. This reaction was applied to 4-methyl-2-nitrobenzaldehyde (135a) so as to study the electron donating effects of the methyl group in the derivative. Initially (Scheme 25) the reaction of 4-methyl-2-nitrobenzaldehyde (135a) with pentane-2,4-dione (136a) in ethereal hydrogen chloride was investigated and afforded a good yield (66%) of a single product identified as the N-hydroxyquinolinone derivative (138a). Further characterisation of the N-hydroxyquinolinone derivative (138a) was provided by its conversion into the N-acetoxy derivative (139) using acetic anhydride. In accord with this proposed N-acetoxy structure (139), the product showed a characteristic⁷² IR carbonyl absorption at 1796cm^{-1} .

The strategy represented in Scheme 25 was extended to synthesising otherwise inaccessible N-hydroxyquinolinone derivatives (138b-e) in general. To this end the reactions of 4-methyl-2-nitrobenzaldehyde (135a) with 1-phenylbutane-1,3-dione (136b), 1,3-diphenylpropane-1,3-dione (136c), ethyl 3-oxobutanoate (136d) and

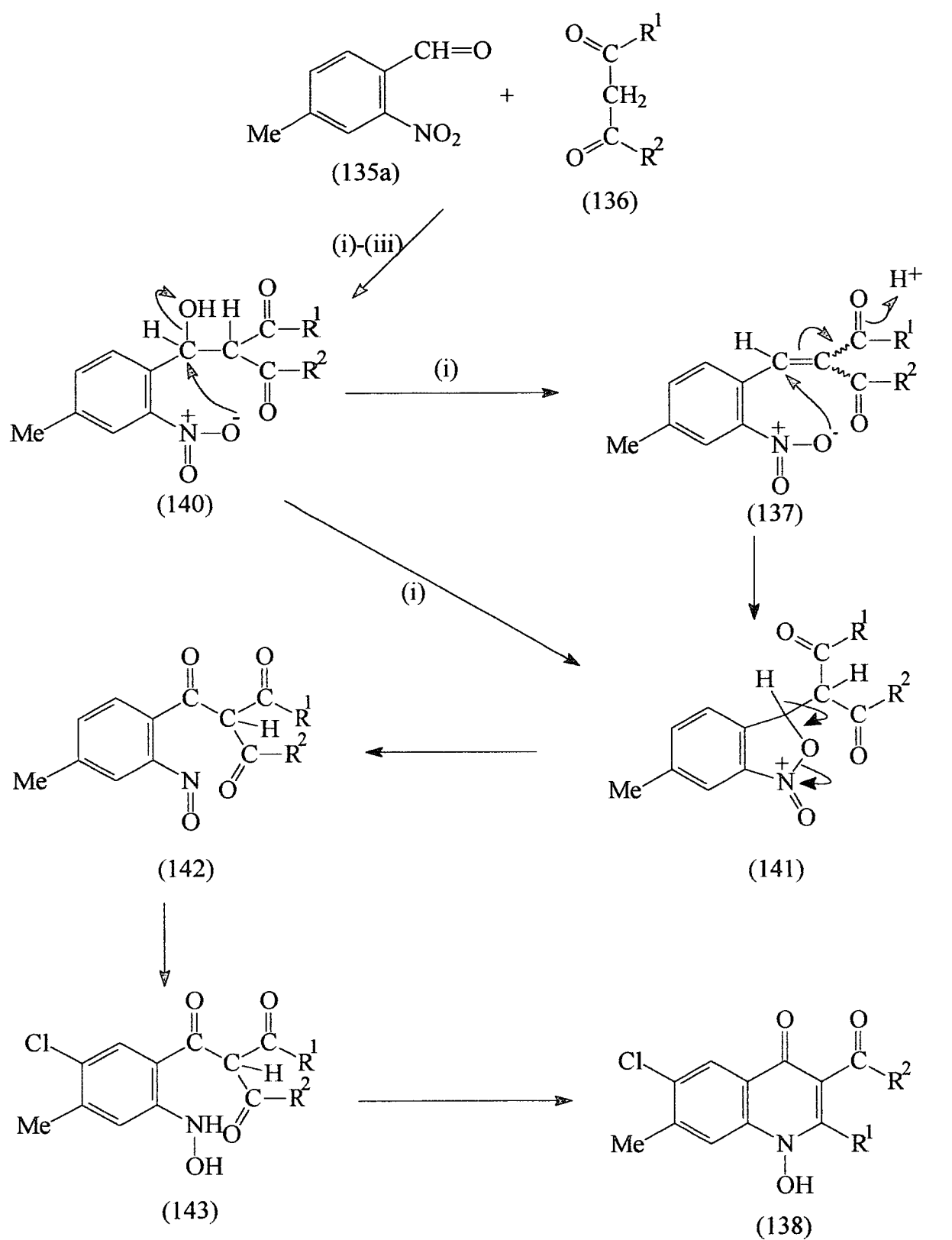
ethyl 3-oxo-3-phenylpropanoate (136e) were investigated in the expectation of initially forming the intermediate nitrobenzylidene derivatives (137b-e) which were hoped would undergo acid- catalysed cyclisation to the corresponding N-hydroxyquinolinone derivatives (138b-e). In practice 4-methyl-2-nitrobenzaldehyde (135a) failed to react with 1-phenylbutane-1,3-dione (136b) in ethereal hydrogen chloride. The 2-nitrobenzaldehyde derivative (135a) also failed to condense with 1,3-diphenylpropane-1,3-dione (136c) in the presence of hydrogen chloride. However 4-methyl-2-nitrobenzaldehyde (135a) reacted with ethyl 3-oxobutanoate (136d) in the presence of hydrogen chloride to afford a product in low yield (30%) whose combustion analysis and mass, IR and ¹H NMR spectra support its formulation as the N-hydroxyquinolinone derivative (138d). In contrast to the acid catalysed reaction of the 2-nitrobenzaldehyde (135a) with ethyl 3-oxobutanoate (136d), the attempted hydrogen chloride catalysed reaction of 4-methyl-2-nitrobenzaldehyde (135a) with ethyl 3-oxo-3-phenylpropanoate (136e) gave a product in low yield (7%) whose combustion analysis and spectroscopic data were consistent with the nitrobenzylidene derivative (137e). It was not possible to determine from the ¹H NMR spectrum of the nitrobenzylidene derivative (137e) which isomer (*E* or *Z*) was isolated from the reaction.

It was apparent (Scheme 25) that 4-methyl-2-nitrobenzaldehyde (135a) was not reacting efficiently with the diacylmethane derivatives (136a-e) in the presence of hydrogen chloride to produce the corresponding N-hydroxyquinolinone derivatives (138a-e). Since these reactions using hydrogen chloride as the catalyst were disappointing, other ways were investigated of obtaining the N-hydroxyquinolinone derivatives (138a-e). Previous work (see Chapter 1, section 3.2, page 18 and Scheme 20) had suggested that a nitrobenzylidene derivative was an intermediate in the acid catalysed reaction of a nitrobenzaldehyde with an active diacylmethane derivative to give a N-hydroxyquinolinone derivative. Also examples in the literature⁶⁶ describe the formation of N-hydroxyquinolinone derivatives directly from the acid catalysed cyclisation reactions of nitrobenzylidene derivatives. The next strategy was therefore to preform the nitrobenzylidene derivatives (137a-e). Since the nitrobenzaldehyde derivative (135a) failed to react efficiently with a diacylmethane derivative (136a-e) in the presence of hydrogen chloride, base catalysis was studied for these

condensation reactions. 4-Methyl-2-nitrobenzaldehyde (135a) reacted with pentane-2,4-dione (136a) using piperidine as the catalyst in dimethoxyethane to give the nitrobenzylidene derivative (137a) in moderate yield. It was anticipated that the nitrobenzylidene derivative (137a) would be converted into the N-hydroxyquinolinone derivative (138a) using hydrogen chloride as the catalyst. However the nitrobenzylidene derivative (137a) reacted with ethereal hydrogen chloride to afford the N-hydroxyquinolinone derivative (138a) in poor yield (5%) together with a substantial amount of the unreacted starting material (137a).

The condensation reaction of 4-methyl-2-nitrobenzaldehyde (135a) with other diacylmethane derivatives (136b-e) using base as the catalyst were carried out to obtain the corresponding nitrobenzylidene derivatives (137b-e). It was anticipated that these nitrobenzylidene derivatives (137b-e) would then react with hydrogen chloride to give the N-hydroxyquinolinone derivatives (138b-e). In practice 4-methyl-2-nitrobenzaldehyde (135a) reacted with 1-phenylbutane-1,3-dione (136b) in the presence of piperidine in glacial acetic acid to afford a product in low yield (38%) which is assigned as the nitrobenzylidene derivative (137b) on the basis of its mass, IR and ^1H NMR spectra and combustion analysis. Extending the reaction time of the piperidine catalysed reaction of the nitrobenzaldehyde (135a) with 1-phenylbutane-1,3-dione (136b) produced the nitrobenzylidene derivative (137b) in high yield (78%). However repeating this reaction in dimethoxyethane instead of glacial acetic acid gave only the nitrobenzylidene derivative (137b) in moderate yield. Unfortunately the attempted conversion of the 2-nitrobenzylidene derivative (137b) into the N-hydroxyquinolinone derivative (138b) in ethereal hydrogen chloride was unsuccessful. Only unreacted starting material (91%) was recovered from the reaction.

Other active diacylmethane derivatives (136c-e) were condensed with 4-methyl-2-nitrobenzaldehyde (135a) to afford nitrobenzylidene derivatives (137c-e) which were thought would undergo acid catalysed cyclisation to the corresponding N-hydroxyquinolinone derivatives (138c-e). In fact 4-methyl-2-nitrobenzaldehyde (135a) condensed with 1,3-diphenylpropane-1,3-dione (136c) in the presence of piperidine in glacial acetic acid to give the nitrobenzylidene derivative (137c) in poor



	<u>R¹</u>	<u>R²</u>
a;	Me	Me
b;	Me	Ph
c;	Ph	Ph
d;	Me	OEt
e;	Ph	OEt

) HCl_(g), ether or DME, 0°C.

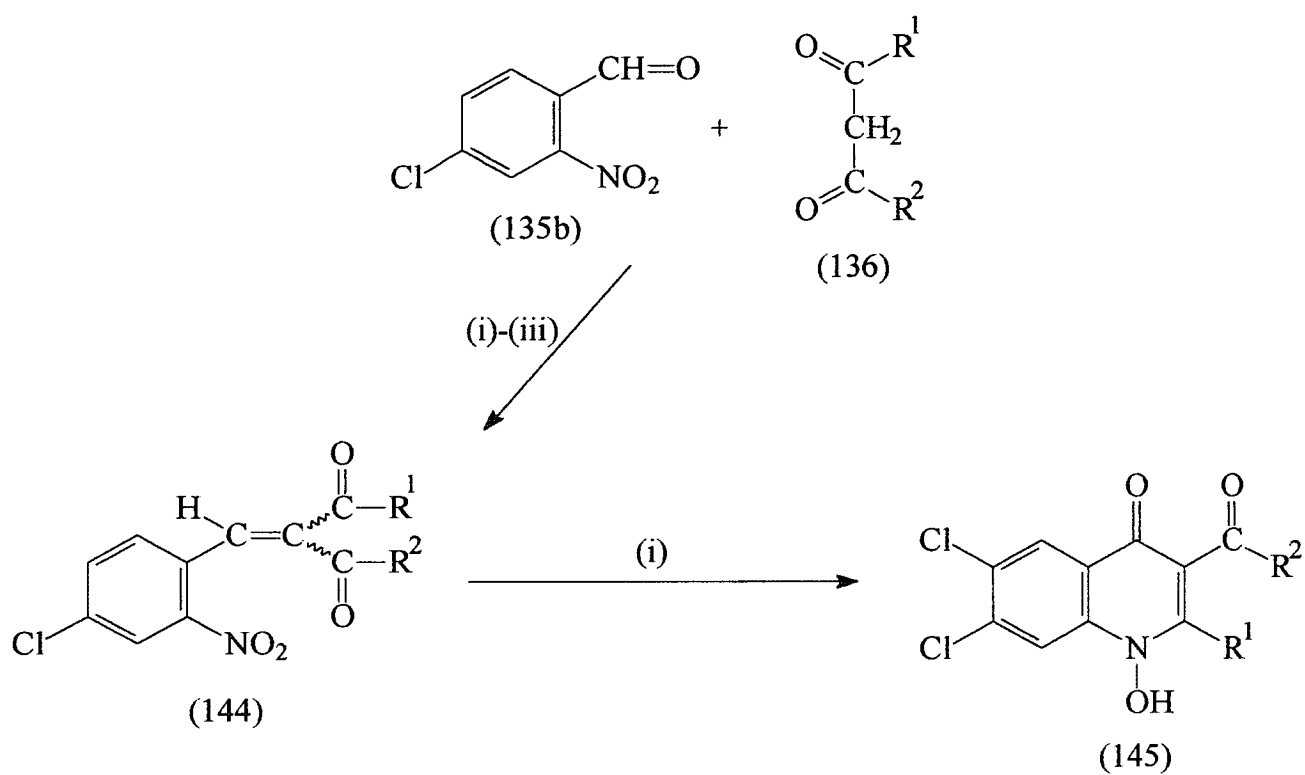
i) piperidine, DME or AcOH, room temp.

ii) NaOEt, EtOH, room temp.

yield (6%). Prolonging the reaction time of the reaction afforded the nitrobenzylidene derivative (137c) also in poor yield. An alternative method was used to condense the nitrobenzaldehyde derivative (135a) with the diacylmethane derivative (136c). However 4-methyl-2-nitrobenzaldehyde (135a) reacted with 1,3-diphenylpropane-1,3-dione (136c) using sodium ethoxide as the catalyst to afford no identifiable product, only the unreacted 2-nitrobenzaldehyde (135a) was isolated in moderate yield. Unfortunately the nitrobenzylidene derivative (137c) was unobtainable in sufficient quantity so as to attempt its conversion into the N-hydroxyquinolinone derivative (138c) in the presence of hydrogen chloride.

Also disappointing was the attempted condensation of 4-methyl-2-nitrobenzaldehyde (135a) with ethyl 3-oxobutanoate (136d) in the presence of piperidine in glacial acetic acid. This reaction gave a mixture of *E* and *Z* isomers of the nitrobenzylidene derivative (137d) in poor yield. The isomeric mixture of the nitrobenzylidene derivative (137d) was established by its combustion analysis and mass, IR and ^1H NMR spectral properties. Significantly the ^1H NMR spectrum of the isomeric *E* and *Z* mixture of the nitrobenzylidene derivative (137d) shows clearly two triplet signals (δ 1.27 and 0.98) attributed to methyl groups attached to a CH_2 group and two quartet signals (δ 4.28 and 4.04) assigned as CH_2 groups connected to methyl groups. Also absorption bands at 1732 and 1716cm^{-1} in the IR spectrum of the isomeric mixture of the nitrobenzylidene derivative (137d) are typical of ester carbonyl groups.

The failure (Scheme 26) of the nitrobenzylidene derivatives (137) to undergo efficient acid catalysed cyclisation to the N-hydroxyquinolinone derivatives (138) suggested that the mechanism of these reactions is more complex than the previously proposed mechanism (see Chapter 1, section 3.2, page 18 and Scheme 20). The initial acid catalysed condensation of the methyl nitrobenzaldehyde (137a) with an active diacylmethane derivative (136) affords the aldol intermediate (140) which may follow possibly two reaction pathways. Firstly nucleophilic attack by the nitro group of the aldol intermediate (140) on the side-chain results in displacement of a hydroxy group and formation of the cyclic intermediate (141). Ring opening of the latter intermediate affords the nitroso intermediate (142) which reacts with hydrogen



	R^1	R^2
a;	Me	Me
b;	Me	Ph
c;	Ph	Ph

(i) $\text{HCl}_{(\text{g})}$, ether or DME, 0°C .

(ii) piperidine, DME or AcOH, room temp.

Scheme 27

chloride to form the hydroxyamine intermediate (143). Cyclisation of the hydroxylamine intermediate (143) accounts for the formation of the N-hydroxy-7-methylquinolinone derivative (138). The second pathway involves the aldol intermediate (140) losing water to afford the methylnitrobenzylidene derivative (137). Nucleophilic attack by the nitro group of the methylnitrobenzylidene derivative (137) on the electrophilic side-chain results in the formation of the same cyclic intermediate (141) as formed directly from the aldol intermediate (140). The cyclic intermediate (141) reacts through the same mechanism as discussed before [(141)→(142)→(143)→(138)] to afford the N-hydroxy-7-methylquinolinone derivative (138).

Attention was next turned (Scheme 27) to synthesising the 6,7-dichloro-N-hydroxyquinolinone derivatives (145) via the acid-catalysed cyclisation reactions of the 4-chloro-2-nitrobenzylidene derivatives (144). The chloro substituent in the nitrobenzylidene derivative (144) is a good example of an electron withdrawing group. It was thought the chloro substituent in the nitrobenzylidene derivatives (144) may cause the para side-chain to become more electrophilic and so react readily with the adjacent nitro group in the presence of hydrogen chloride to afford the N-hydroxyquinolinone derivatives (145). Initially (Scheme 24) 4-chloro-2-nitrobenzaldehyde (135b) was synthesised using the same method as for the formation of 4-methyl-2-nitrobenzaldehyde (135a). 4-Chloro-2-nitrotoluene (133b) was converted into the 2-nitrobenzaldehyde derivative (135b) in good yield in two steps [(133b)→(134b)→(135b)].

Investigations (Scheme 27) centred on the reaction of 4-chloro-2-nitrobenzaldehyde (135b) with pentane-2,4-dione (136a) in the presence of hydrogen chloride. It was anticipated that the reaction would lead to the formation of the N-hydroxyquinolinone derivative (145a). In practice 4-chloro-2-nitrobenzaldehyde (135b) reacted with pentane-2,4-dione (136a) in ethereal hydrogen chloride to afford the N-hydroxyquinolinone derivative (145a) in low yield (17%) and the nitrobenzylidene derivative (144a) in moderate yield (49%). The combustion analysis and spectroscopic properties of the products (144a) and (145a) were fully in accord with their assigned structures. Repeating the acid-catalysed reaction of the 2-

nitrobenzaldehyde (135b) with pentane-2,4-dione (136a) over a longer reaction time also gave the N-hydroxyquinolinone derivative (145a) and the nitrobenzylidene derivative (144a) each in low yields. The inefficiency of this reaction was thought to be attributable to insufficient hydrogen chloride present in the reaction mixture. It was hoped that a high concentration of hydrogen chloride present in the reaction of the 2-nitrobenzaldehyde (135b) with pentane-2,4-dione (136a) would afford the N-hydroxyquinolinone derivative (145a) in high yield. However in practice 4-chloro-2-nitrobenzaldehyde (135b) reacted with the diacylmethane derivative (136a) in excess ethereal hydrogen chloride to give the N-hydroxyquinolinone derivative (145a) and the nitrobenzylidene derivative (144a) each in low yields.

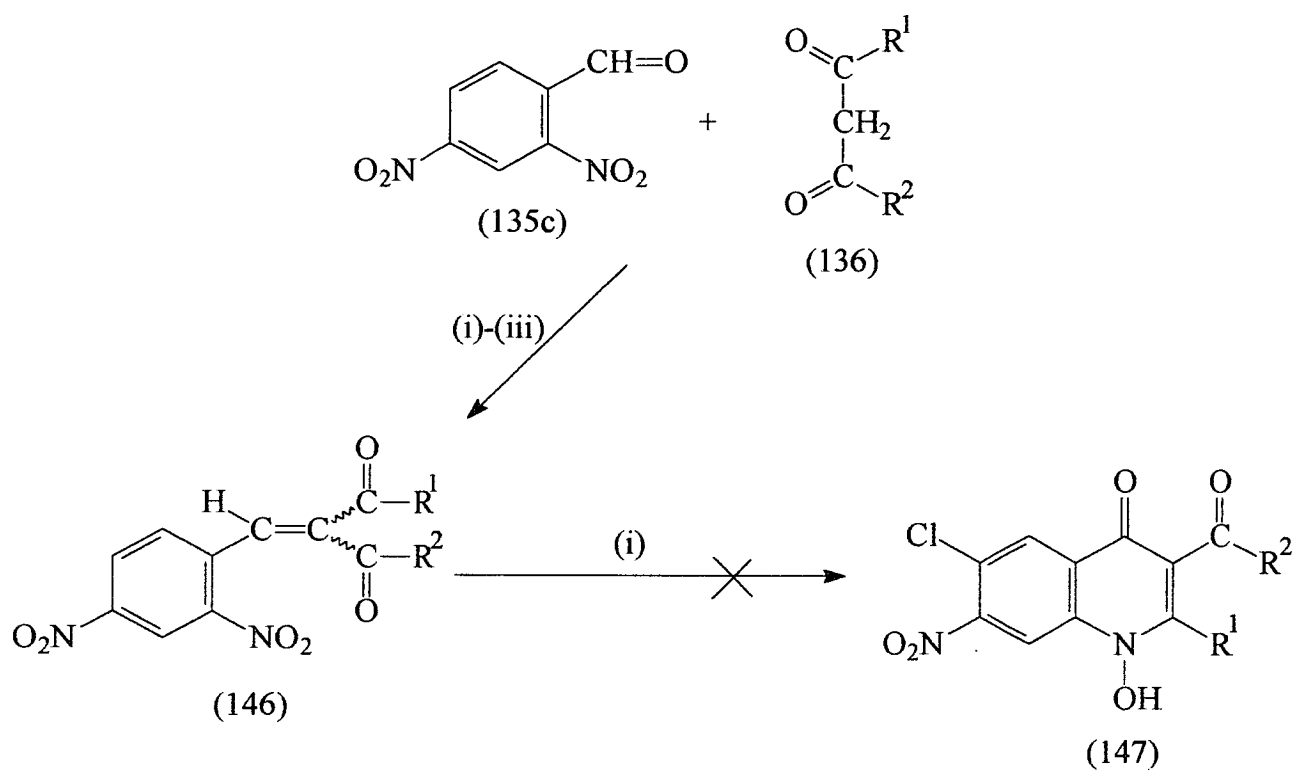
Similar to the 4-methylbenzaldehyde derivative (135a), the 4-chlorobenzaldehyde derivative (135b) was inefficiently reacting with a diacylmethane derivative (136) in ethereal hydrogen chloride to afford the corresponding N-hydroxyquinolinone derivative (145). Attention was turned to preforming the nitrobenzylidene derivatives (144a-c) since derivatives of this type are known⁶⁶ to cyclise to N-hydroxyquinolinone derivatives in the presence of hydrogen chloride. The condensation of 4-chloro-2-nitrobenzaldehyde (135b) with the active diacylmethane derivative (136) was carried out in the presence of base to give the required nitrobenzylidene derivative (144). The 2-nitrobenzaldehyde (135b) reacted with pentane-2,4-dione (136a) in the presence of piperidine in glacial acetic acid to afford the nitrobenzylidene derivative (144a) in low yield. Repeating this reaction in dimethoxyethane instead of glacial acetic acid also gave the nitrobenzylidene derivative (144a) in low yield. It was found that extending the reaction time of the reaction of 4-chloro-2-nitrobenzaldehyde (135b) with pentane-2,4-dione (136a) in the presence of piperidine gave the nitrobenzylidene derivative (144a) in good yield. Disappointingly the nitrobenzylidene derivative (144a) failed to react with ethereal hydrogen chloride to produce the expected N-hydroxyquinolinone derivative (145a), but instead the nitrobenzylidene derivative (144a) was recovered in quantitative yield.

The synthesis (Scheme 27) of other nitrobenzylidene derivatives (144b-c) were carried out in the expectation that these nitrobenzylidene derivatives (144b-c) would

undergo acid- catalysed cyclisation to the N-hydroxyquinolinone derivatives (145b-c). 4-Chloro-2-nitrobenzaldehyde (135b) reacted with 1-phenylbutane-1,3-dione (136b) in the presence of piperidine in glacial acetic acid to afford a product in low yield which was identified on the basis of its combustion analysis and mass, IR, ^1H and ^{13}C NMR spectra as the nitrobenzylidene derivative (144b). The exact configuration (*E* or *Z*) of the nitrobenzylidene derivative (144b) is not known. The ^{13}C NMR spectrum of the nitrobenzylidene derivative (144b) shows only one isomer is present. It is more likely that the *E* isomer of the nitrobenzylidene derivative (144b) has been synthesised since this would be the more thermodynamically stable derivative.

Attempts were made to improve the condensation reaction between the 2-nitrobenzaldehyde (135b) and the diacylmethane derivative (136b) in the expectation of efficiently forming the nitrobenzylidene derivative (144b). Prolonging the reaction time of the reaction of 4-chloro-2-nitrobenzaldehyde (135b) with 1-phenylbutane-1,3-dione (136b) in the presence of piperidine in glacial acetic acid afforded the nitrobenzylidene derivative (144b) in good yield (70%). Repeating this reaction in dimethoxyethane instead of glacial acetic acid also gave the nitrobenzylidene derivative (144b) in good yield. Disappointingly the nitrobenzylidene derivative (144b) failed to cyclise to the N-hydroxyquinolinone derivative (145b) in the presence of ethereal hydrogen chloride. Instead only unreacted nitrobenzylidene derivative (144b) was isolated from the reaction. Extending the reaction time of the reaction of the nitrobenzylidene derivative (144b) with ethereal hydrogen chloride also failed to give the N-hydroxyquinolinone derivative (145b), only unreacted starting material being isolated from the reaction.

Attempts were made to synthesise the nitrobenzylidene derivative (144c). It was hoped that the nitrobenzylidene derivative (144c) would cyclise to the N-hydroxyquinolinone derivative (145c) in the presence of hydrogen chloride. In practice the piperidine catalysed reaction of 4-chloro-2-nitrobenzaldehyde (135b) with 1,3-diphenylpropane-1,3-dione (136c) in glacial acetic acid gave a product in poor yield whose combustion analysis and spectroscopic properties were consistent with its formulation as the 2-nitrobenzylidene derivative (144c). In contrast



	$\underline{R^1}$	$\underline{R^2}$
a;	Me	Me
b;	Me	Ph

(i) $\text{HCl}_{(g)}$, ether or DME, 0°C .

(ii) piperidine, DME or AcOH, room temp. or 0°C .

Scheme 28

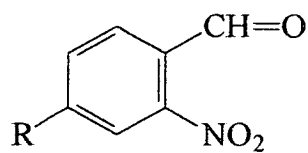
increasing the reaction time of the condensation reaction gave the nitrobenzylidene derivative (144c) in good yield. Unfortunately due to lack of time it was not possible to try and obtain the N-hydroxyquinolinone derivative (145c) by reaction of the nitrobenzylidene derivative (144c) with ethereal hydrogen chloride.

Investigations (Scheme 28) on the acid- catalysed cyclisation reaction of the 2,4-dinitrobenzylidene derivatives (146a and b) to the corresponding N-hydroxyquinolinone derivatives (147a and b) were carried out in parallel to the work done on the 4-methyl and 4-chloro nitrobenzylidene derivatives (137) and (144). The nitro group para to the side- chain in these nitrobenzylidene derivatives (146a and b) is strongly electron withdrawing. It was thought that the para nitro group in the nitrobenzylidene derivatives (146a and b) would draw electron density away from the side- chain and so make the side- chain more electrophilic and prone to reaction with the adjacent nitro group. In essence it was hoped that the nitrobenzylidene derivatives (146a and b) would cyclise to the corresponding N-hydroxyquinolinone derivatives (147a and b) in the presence of hydrogen chloride more readily than when the methyl or chloro nitrobenzylidene derivatives (137) and (144) were converted into the N-hydroxy products (138) and (145) under the same reaction conditions. The strategy (Scheme 24) was to initially synthesise 2,4-dinitrobenzaldehyde (135c) and this was accomplished using the same method utilised to obtain the 4-methyl and 4-chloro benzaldehyde derivatives (135a) and (135c). 2,4-Dinitrotoluene (133c) was converted into the 2,4-dinitrobenzaldehyde (135c) in high yield in two steps [(133c)→(134c)→(135c)].

In comparison with the acid catalysed reactions of pentane-2,4-dione (136a) with the methyl or chloro nitrobenzaldehyde derivatives (135a) or (135b), the hydrogen chloride catalysed (Scheme 28) reaction of 2,4-dinitrobenzaldehyde (135c) with pentane-2,4-dione (136a) in dimethoxyethane failed to afford the N-hydroxyquinolinone derivative (146a). Instead the reaction gave the unreacted 2-nitrobenzaldehyde (135c) in low yield together with an oil in high yield (63%) whose combustion analysis and mass, IR and ¹H NMR spectra were consistent with its formulation as the nitrobenzylidene derivative (146a). Since the acid- catalysed reaction of 2,4-dinitrobenzaldehyde (135c) with pentane-2,4-dione (136a) failed to

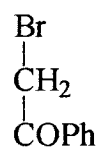
afford the N-hydroxyquinolinone derivative (147a) it was decided to change the strategy and preform the nitrobenzylidene derivative (146a). It was thought that treating the nitrobenzylidene derivative (146a) with hydrogen chloride would lead to the formation of the N-hydroxyquinolinone derivative (147a). Previous studies⁶⁶ had shown that nitrobenzylidene derivatives react in the presence of ethereal hydrogen chloride to afford N-hydroxyquinolinone derivatives. 2,4-Dinitrobenzaldehyde (135c) condensed with pentane-2,4-dione (136a) in the presence of piperidine in glacial acetic acid to afford the nitrobenzylidene derivative (146a) in low yield. However repeating the condensation reaction at 0°C instead of room temperature gave the nitrobenzylidene derivative (146a) in moderate yield (39%). It was found that carrying out the condensation reaction in a different solvent gave the nitrobenzylidene derivative (146a) in good yield. The piperidine catalysed reaction of 2,4-dinitrobenzaldehyde (135c) with pentane-2,4-dione (136a) in dimethoxyethane afforded the nitrobenzylidene derivative (146a) in good yield as well as some of the unreacted 2,4-dinitrobenzaldehyde (135c). Similar to the acid- catalysed reactions of the chloro and methyl nitrobenzylidene derivatives (137) and (144), the nitrobenzylidene derivative (146a) also failed to be converted into the corresponding N-hydroxyquinolinone derivative (147a) using hydrogen chloride as the catalyst. Only unreacted starting material was recovered from the reaction.

Further investigations were carried out on the base catalysed condensation reactions of 2,4-dinitrobenzaldehyde (135c) with other diacylmethane derivatives (136). It was hoped that the nitrobenzaldehyde derivative (135c) would condense with 1-phenylbutane-1,3-dione (135b) to give the nitrobenzylidene derivative (146b). It was anticipated that the nitrobenzylidene derivative (146b) would be converted into the N-hydroxyquinolinone derivative (147b) in the presence of ethereal hydrogen chloride. In practice however the reaction (Scheme 28) of 2,4-dinitrobenzaldehyde (135c) with 1-phenylbutane-1,3-dione (136b) in the presence of piperidine gave the nitrobenzylidene derivative (146b) as an oil in moderate yield (47%) together with a substantial amount of unreacted 2,4-dinitrobenzaldehyde (135b). The accurate mass, IR and ¹H NMR spectra of the nitrobenzylidene derivative (146b) were fully in accord with its assigned structure. Extending the reaction time of the piperidine catalysed condensation reaction of 2,4-dinitrobenzaldehyde (135c) with



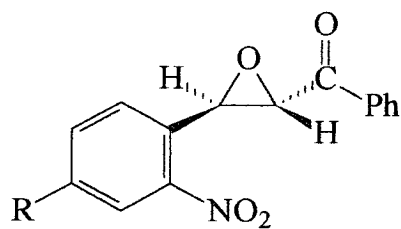
(135)

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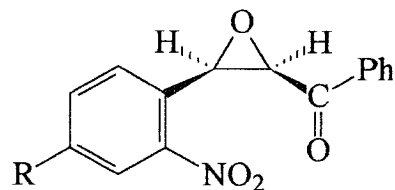
(148)

(i)



(149)

(i)



(150)

R
a; Me
b; Cl
c; NO₂

(i) NaOMe, MeOH, room temp.

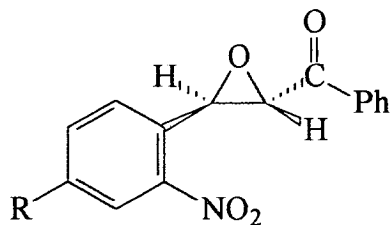
Scheme 29

1-phenylbutane-1,3-dione (136b) gave the nitrobenzylidene derivative (146b) in good yield (77%). Unfortunately investigations on the acid- catalysed cyclisation reaction of the nitrobenzylidene derivative (146b) were terminated at this point due to time constraints.

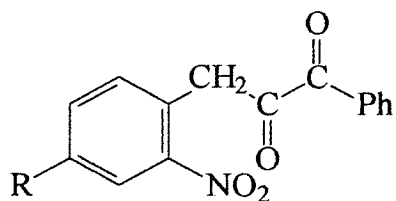
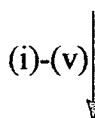
3. STUDIES ON THE SCOPE OF THE ACID- CATALYSED CYCLISATION REACTIONS OF 2-NITROPHENYLOXIRANE DERIVATIVES TO 1,3-DIHYDROXY 4-QUINOLONES

Substituted 2-nitrophenyloxirane derivatives are known⁶⁷ to undergo acid- catalysed cyclisation to dihydroxyquinolinone derivatives as discussed earlier (see Chapter 1, section 3.2, page 19 and Scheme 21). 2-Nitrophenyloxirane derivatives are suitable reagents for this type of acid- catalysed reaction because the protonated oxirane ring within the side- chain of these derivatives makes the side- chain susceptible to nucleophilic attack by the adjacent nitro group. It was hoped this method would be more successful than that of the acid- catalysed cyclisation reactions of nitrobenzylidene derivatives to N-hydroxyquinolinone derivatives. Investigations were carried out on the substituent effects in nitrophenyloxirane derivatives with regard to the effect on the acid- catalysed cyclisation of these derivatives to dihydroxyquinolinone derivatives. It was thought that an electron donating group para to the side- chain in a nitrophenyloxirane derivative would reduce the electrophilic nature of the side- chain and so inhibit the nucleophilic attack by the nitro group on the ortho side- chain in the presence of hydrogen chloride. Consequently this was expected to result in the isolation of dihydroxyquinolinone derivatives in low yields. In contrast an electron withdrawing group para to the side- chain in a nitrophenyloxirane derivative might enhance the electrophilic nature of the side- chain and so the nitrophenyloxirane derivative may react readily in the presence of hydrogen chloride to afford a dihydroxyquinolinone derivative in high yield.

The initial strategy for investigating the substituent effects in the acid- catalysed cyclisation reactions of nitrophenyloxirane derivatives to dihydroxyquinolinone derivatives involved the synthesis (Scheme 29) of the *trans* 4-methyl-2-nitrophenyloxirane derivative (149a). The para methyl group in the

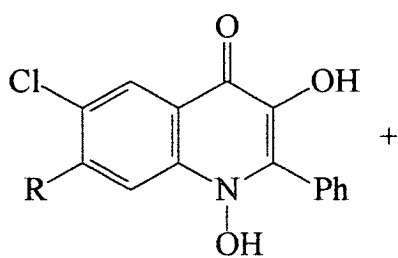


(149)



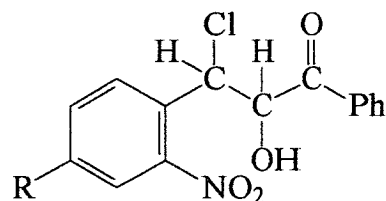
(151)

+

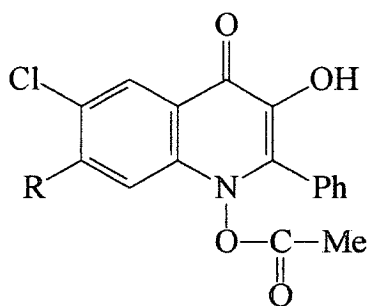
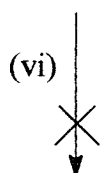


(152)

+



(153)



(154)

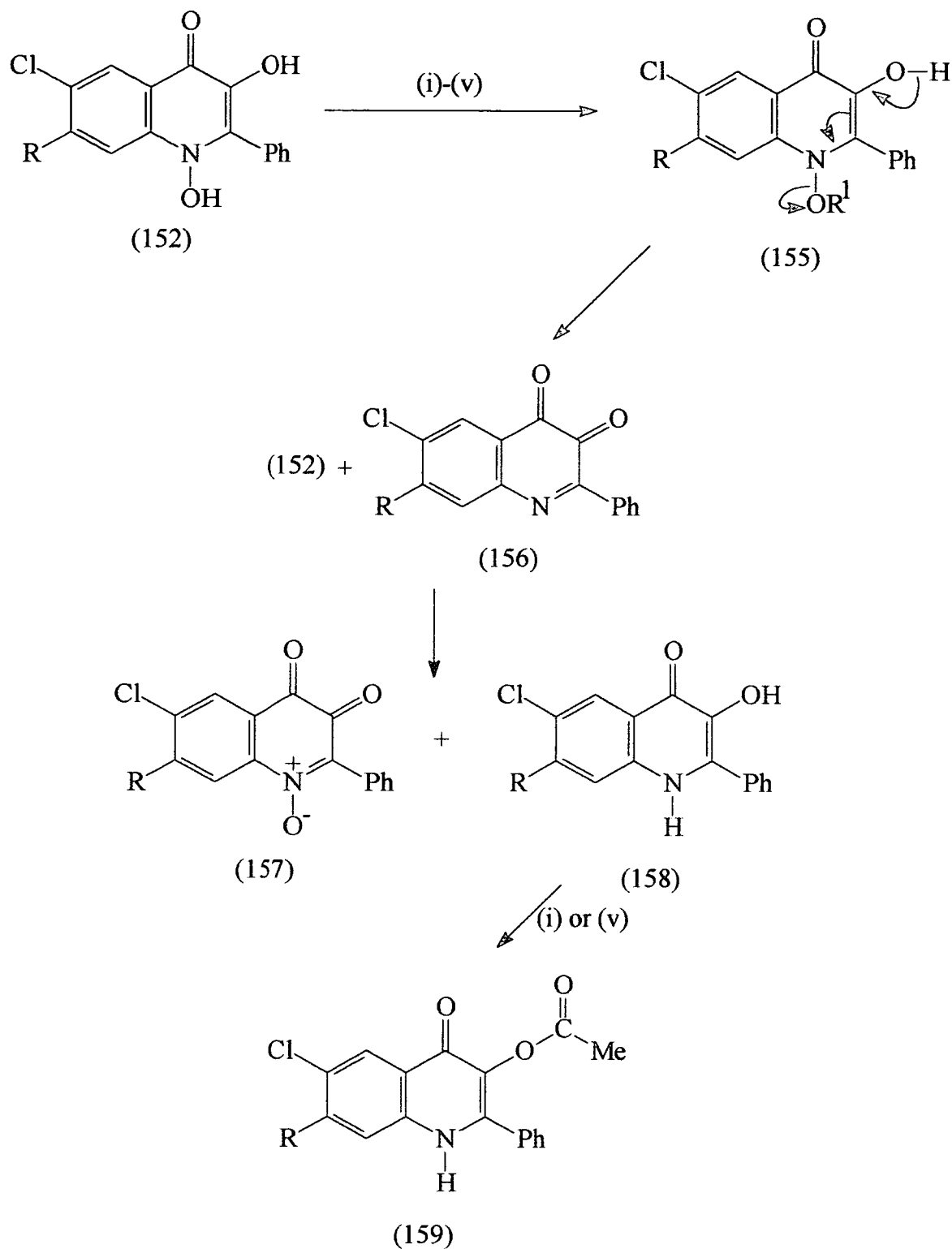
R
a; Me
b; Cl
c; NO₂

- (i) HCl_(g), dioxane, 11°C.
(ii) HCl_(g), DME or AcOH or DCM, 0°C.
(iii) HCl_(g), BF₃.Et₂O, DME, 0°C.
(iv) HCl_(g), PhCH₂N⁺Et₃Cl⁻, DCM, 0°C.
(v) HCl_(g), hydroquinone, dioxane, 11°C.
(vi) Ac₂O, 100°C or reflux.

Scheme 30

nitrophenyloxirane derivative (149a) is a good example of an electron donating group. *Trans* nitrophenyloxirane derivatives are known⁷³ to be the products from the reactions of 2-nitrobenzaldehyde derivatives with 2-bromoacetophenone in methanolic sodium methoxide. 4-Methyl-2-nitrobenzaldehyde (135a) reacted smoothly with 2-bromoacetophenone (148) in methanolic sodium methoxide to afford the expected *trans* nitrophenyloxirane derivative (149a) in good yield (72%) whose combustion analysis and spectroscopic data were in agreement with its proposed structure. Significantly the ¹H NMR spectrum of the *trans* nitrophenyloxirane derivative (149a) showed oxirane ring proton coupling constants (J_{2,1}) in agreement with the *trans* configuration. The reaction (Scheme 30) of the *trans* nitrophenyloxirane derivative (149a) with hydrogen chloride in dioxane afforded the hydrochloride salt of the dihydroxyquinolinone derivative (152a) in moderate yield (45%) whose combustion analysis and IR and ¹H NMR spectra were consistent with its structure. The mass spectrum of the hydrochloride salt of the dihydroxyquinolinone derivative (152a) showed no parent ion peak attributable to the hydrochloride salt of the dihydroxyquinolinone derivative (152a). However a peak at m/z 301 in the mass spectrum of the hydrochloride salt of the dihydroxyquinolinone derivative (152a) is consistent with the dihydroxyquinolinone derivative (152a) (ie loss of hydrogen chloride). Neutralising the hydrochloride salt of the dihydroxyquinolinone derivative (152a) afforded the free dihydroxyquinolinone derivative (152a) which had combustion analysis and spectroscopic properties in accord with its structure.

Since the hydrogen chloride catalysed reaction of the *trans* nitrophenyloxirane derivative (149a) to the dihydroxyquinolinone derivative (152a) was rather disappointing other reaction conditions were investigated in an attempt to find efficient methods of synthesising the dihydroxyquinolinone derivative (152a). Initially any possible solvent effects were investigated in the acid- catalysed cyclisation reactions of the nitrophenyloxirane derivative (149a) to the dihydroxyquinolinone derivative (152a). The *trans* nitrophenyloxirane derivative (149a) reacted with hydrogen chloride in dimethoxyethane (instead of dioxane) to afford the dihydroxyquinolinone derivative (152a) in moderate yield (57%) together with a second product in low yield (16%) whose combustion analysis and



Scheme 31

spectroscopic data allow its formulation as the diketone derivative (151a). The high carbonyl band at 1716cm^{-1} in the IR spectrum of the diketone derivative (151a) can be attributed to the enhanced effect of two carbonyl groups being adjacent to one another. It is therefore less likely that the product isolated was the isomeric 1-phenyl-3-(4-methyl-2-nitrophenyl)propane-1,3-dione. Formation of the diketone derivative (151a) is from the known⁷⁴ acid-catalysed rearrangement reaction of nitrophenyloxirane derivatives.

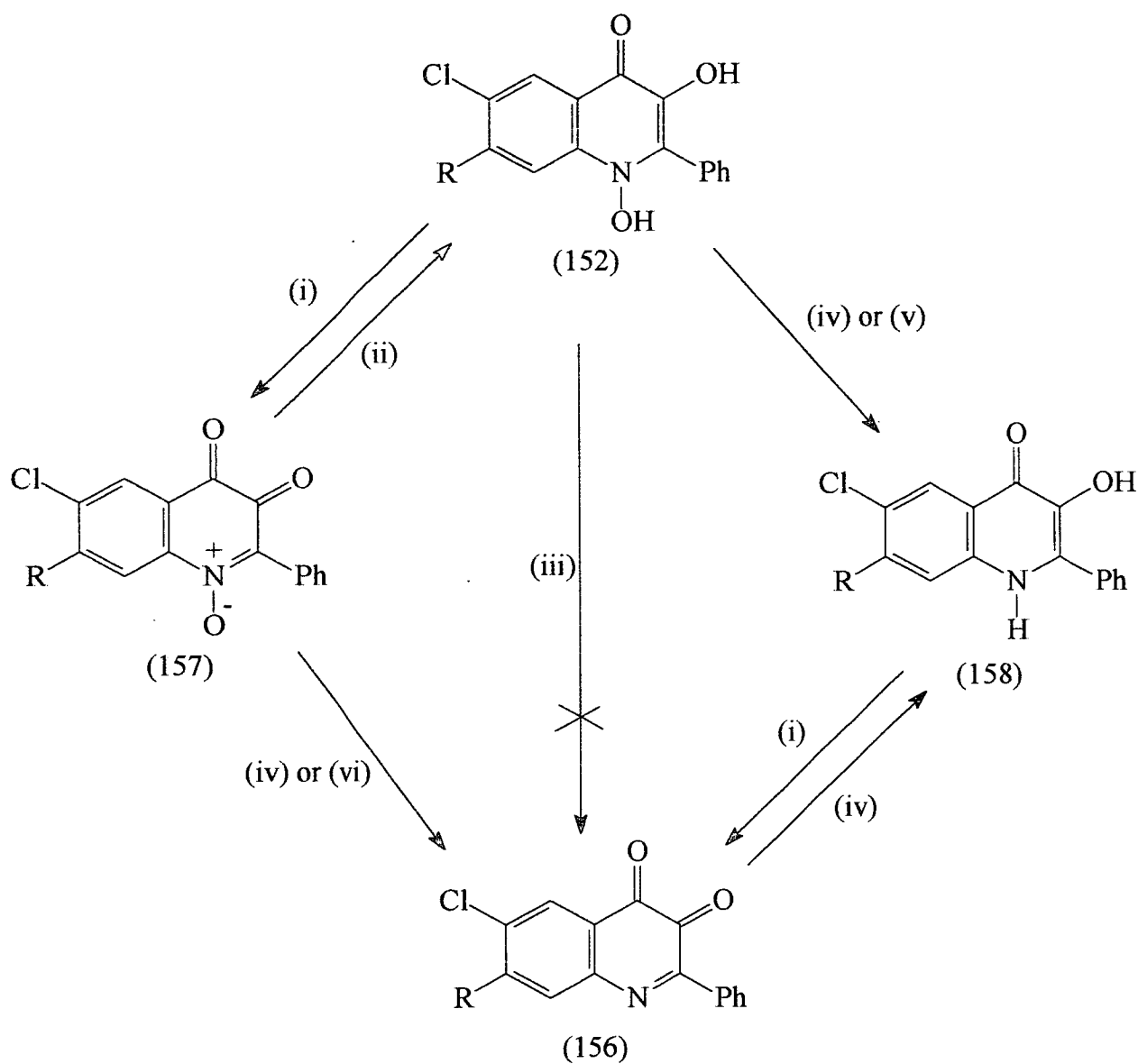
Other solvents were investigated in the hydrogen chloride catalysed cyclisation reaction of the nitrophenyloxirane derivative (149a) to the dihydroxyquinolinone derivative (152a). The nitrophenyloxirane derivative (149a) reacted with hydrogen chloride in glacial acetic acid to give the hydrochloride salt of the dihydroxyquinolinone derivative (152a) in poor yield (35%) as the only identifiable product. However repeating the reaction in dichloromethane instead of glacial acetic acid afforded the hydrochloride salt of the dihydroxyquinolinone derivative (152a) in moderate yield as well as (Scheme 31) the N-oxide derivative (157a) in low yield (5%). The N-oxide derivative (157a) analysed correctly and had spectroscopic properties in agreement with its structure. The formation of the N-oxide derivative in the reaction of the nitrophenyloxirane derivative (149a) with hydrogen chloride is unclear since there is no oxidising agent present in the reaction mixture. The likely formation of the N-oxide derivative (157a) would be from aerial oxidation of the parent dihydroxyquinolinone derivative (152a) initially formed in the reaction.

An attempt was made to obtain the dihydroxyquinolinone derivative (152a) in high yield by incorporating a Lewis acid into the reaction of hydrogen chloride with the nitrophenyloxirane derivative (149a). It was thought the Lewis acid would complex to the oxirane ring of the nitrophenyloxirane derivative (149a) and draw electron density away from the oxirane ring. As a consequence the oxirane ring would become more electrophilic and might react readily with the ortho nitro group in the presence of hydrogen chloride to ultimately give the dihydroxyquinolinone derivative (152a). In practice though the *trans* nitrophenyloxirane derivative (149a) was not converted into the dihydroxyquinolinone derivative (152a) in the presence of hydrogen chloride and boron trifluoride etherate, instead the reaction affording only

the N-oxide derivative (157a) in low yield. As discussed earlier the N-oxide (157a) may be obtained from the aerial oxidation of the dihydroxyquinolinone derivative (152a) which is initially formed in the reaction of the nitrophenyloxirane derivative (149a) with hydrogen chloride.

A further attempt was made to efficiently synthesise the dihydroxyquinolinone derivative (152a) from the nitrophenyloxirane derivative (149a). As described earlier the proposed mechanism of the reaction of nitrophenyloxirane derivative (149a) with hydrogen chloride (see Chapter 1, section 3.2, page 19 and Scheme 21) involves a step where a nitroso intermediate reacts with hydrogen chloride to afford a hydroxylamino intermediate, cyclisation of which gives the dihydroxyquinolinone derivative (152a). It was thought that the concentration of chloride ion present in the reaction mixture may effect the rate of conversion of the nitroso intermediate into the hydroxylamino intermediate. If the rate of formation of the hydroxylamino intermediate could be increased it may therefore lead to the isolation of the dihydroxyquinolinone derivative (152a) in high yield. In practice benzyl triethylammonium chloride was used as a suitable source of chloride ion. However the hydrogen chloride catalysed reaction of the nitrophenyloxirane derivative (149a) in the presence of benzyl triethylammonium chloride failed to afford the dihydroxyquinolinone derivative (152a), instead the reaction gave no identifiable material.

Attempts (Scheme 30) were made to prove the structure of the dihydroxyquinolinone derivative (152a). The dihydroxyquinolinone derivative (152a) was expected to react with acetic anhydride to give the simple N-acetoxy derivative (154a). However (Scheme 31) heating the dihydroxyquinolinone derivative (152a) under reflux in acetic anhydride failed to afford the N-acetoxy derivative (154a). This reaction gave instead the 3-acetoxyquinolinone derivative (159a) in low yield (21%) whose accurate mass and ^1H NMR spectra were in agreement with its structure. The IR spectrum of the 3-acetoxy derivative (159a) showed absorption at 1767cm^{-1} attributed to the carbonyl of the 3-acetoxy group. It was thought that the forcing conditions of heating the dihydroxyquinolinone derivative (152a) under reflux in acetic anhydride may have been too harsh. Repeating this reaction at 100°C also



R
a; Me
b; Cl
c; NO₂

- (i) MnO₂, THF or DMF, room temp.
(ii) H₂, Pd/C, dioxane, atmos. press.
(iii) H₂SO₄ (conc.), room temp.
(iv) Na₂S₂O₄, EtOH, H₂O, reflux.
(v) H₂, Pd/C, EtOH or AcOH, atmos. press.
(vi) POCl₃, reflux.

Scheme 32

failed to give the N-acetoxyquinolinone derivative (154a) and gave instead an inseparable red mixture, tentatively identified by IR and ^1H NMR spectra as the 3-acetoxy derivative (159a) and the N-oxide derivative (157a). Evidence (Scheme 32) for the N-oxide derivative (157a) was obtained from its synthesis by oxidation of the parent dihydroxyquinolinone derivative (152a). Treatment of the dihydroxyquinolinone derivative (152a) with activated manganese dioxide in dimethylformamide afforded the corresponding N-oxide (157a) in excellent yield.

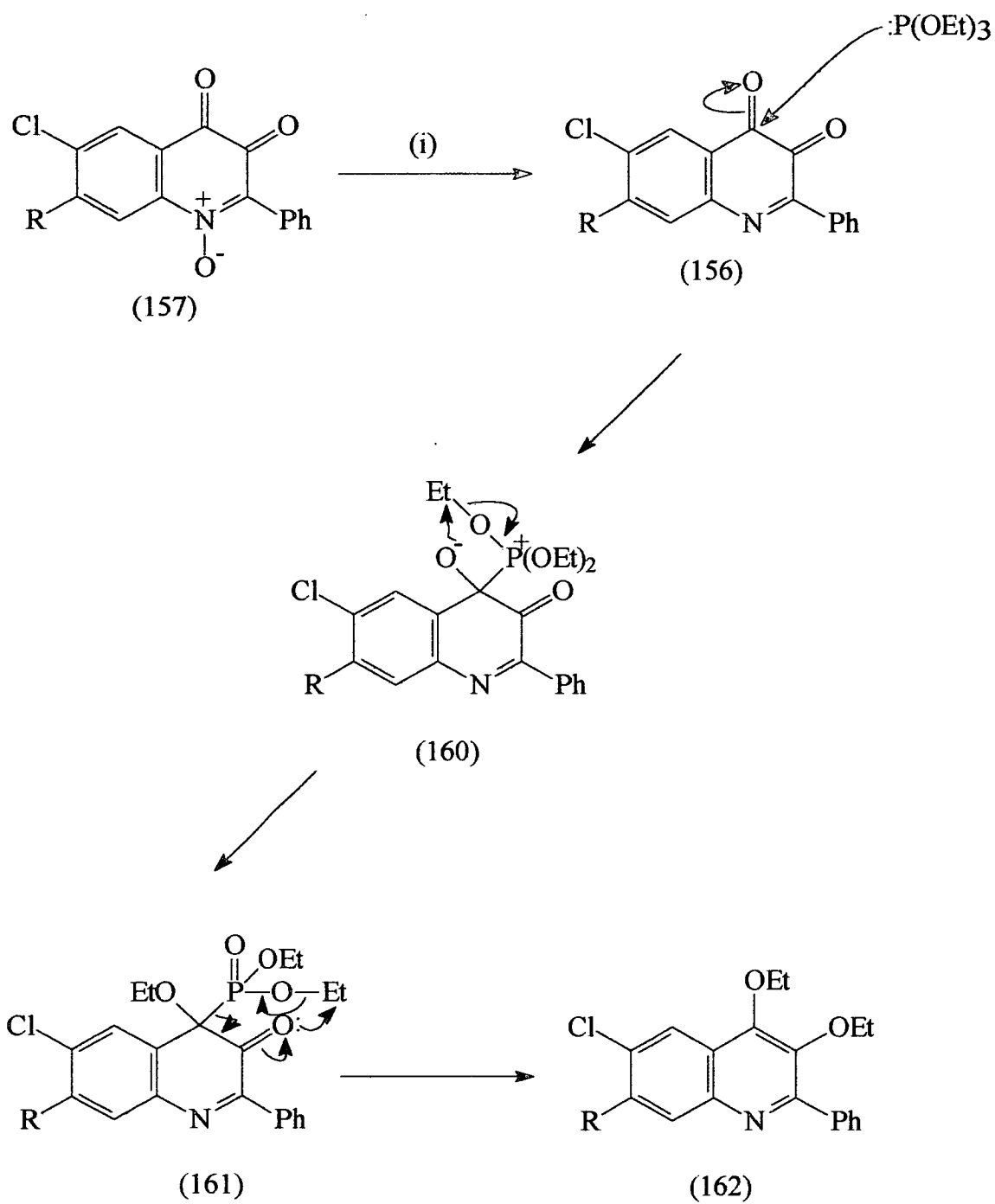
Since a simple N-acetoxy derivative (154a) could not be formed by reaction of the dihydroxyquinolinone derivative (152a) with acetic anhydride, other ways were investigated to prove the structure of the dihydroxyquinolinone derivative (152a). In fact the dihydroxyquinolinone derivative (152a) should be easily reduced to the 3-hydroxyquinolinone derivative (158a). In practice heating the dihydroxyquinolinone derivative (152a) with sodium dithionite under reflux in aqueous ethanol gave the 3-hydroxyquinolinone derivative (158a) in good yield whose combustion analysis and spectroscopic properties were in accord with its assigned structure. The proposed mechanism of the reaction of the dihydroxyquinolinone derivative (152a) with acetic anhydride involves the initial formation of the N-acetoxy derivative (155a; $\text{R}^1=\text{COMe}$). The N-acetoxy derivative (155a; $\text{R}^1=\text{COMe}$) loses the acetoxy group via elimination of glacial acetic acid to afford the 3,4-dioxoquinolinone derivative (156a). It is then thought that the 3,4-dioxoquinolinone derivative (156a) is reduced to the 3-hydroxyquinolinone derivative (158a) by reaction with unreacted dihydroxyquinolinone derivative (152a). Consequently oxidation of the dihydroxyquinolinone derivative (152a) involved in the reduction of the 3,4-dioxoquinolinone derivative (156a) accounts for the formation of the N-oxide derivative (157a). Finally the 3-hydroxyquinolinone derivative (158a) undergoes further reaction with acetic anhydride to give the isolated 3-acetoxy quinolinone derivative (159a).

Investigations were carried out on the proposed mechanism of the reaction of the dihydroxyquinolinone derivative (152a) with acetic anhydride. These studies involved using other leaving groups similar to an acetoxy group. It was expected that the dihydroxyquinolinone derivative (152a) would react with tosyl chloride to afford

a mixture of the N-oxide (157a) and the 3-hydroxyquinolinone derivative (158a). In practice the dihydroxyquinolinone derivative (152a) reacted with tosyl chloride in the presence of triethylamine to afford the N-oxide derivative (157a) and the 3-hydroxyquinolinone derivative (158a) each in moderate yields. Further evidence was sought in support of the mechanism outlined in Scheme 31 to show that the mechanism was general and independent of the leaving group involved. The reaction of the dihydroxyquinolinone derivative (152a) with ethyl chloroformate was carried out in the anticipation that ethyl chloroformate would behave in a similar fashion to acetic anhydride and tosyl chloride. It was found that the dihydroxyquinolinone derivative (152a) reacted with ethyl chloroformate in the presence of triethylamine to afford the N-oxide derivative (157a) and the 3-hydroxyquinolinone derivative (158a) each in moderate yields. Phenylisocyanate was utilised as a source of a leaving group similar to acetic anhydride, tosyl chloride and ethyl chloroformate. However the reaction of the dihydroxyquinolinone derivative (152a) with phenylisocyanate afforded only the N-oxide (157a) in low yield. There was no evidence in the reaction for the formation of the 3-hydroxyquinolinone derivative (158a).

Further studies were carried out on the reaction mechanism involved in the conversion of the dihydroxyquinolinone derivative (152a) into the N-oxide (157a) and the 3-hydroxyquinolinone (158a) derivatives using various reagents containing good leaving groups. The dihydroxyquinolinone derivative (152a) was treated with just base to see if it could undergo base catalysed dehydration to the 3,4-dioxoquinolinone derivative (156a). The 3,4-dioxoquinolinone derivative (156a) was then expected to react with unreacted dihydroxyquinolinone derivative (152a) to afford a mixture of the N-oxide and the 3-hydroxyquinolinone derivatives (157a) and (158a). However the triethylamine catalysed dehydration reaction of the dihydroxyquinolinone derivative (152a) afforded only very small quantities of the corresponding N-oxide and 3-hydroxyquinolinone derivatives (157a) and (158a) as the isolated products.

Attempts were made to obtain the 3,4-dioxoquinolinone derivative (156a) which is proposed as an intermediate in the mechanism outlined in Scheme 31. It was thought the N-oxide derivative (157a) could be reduced to the 3,4-dioxoquinolinone



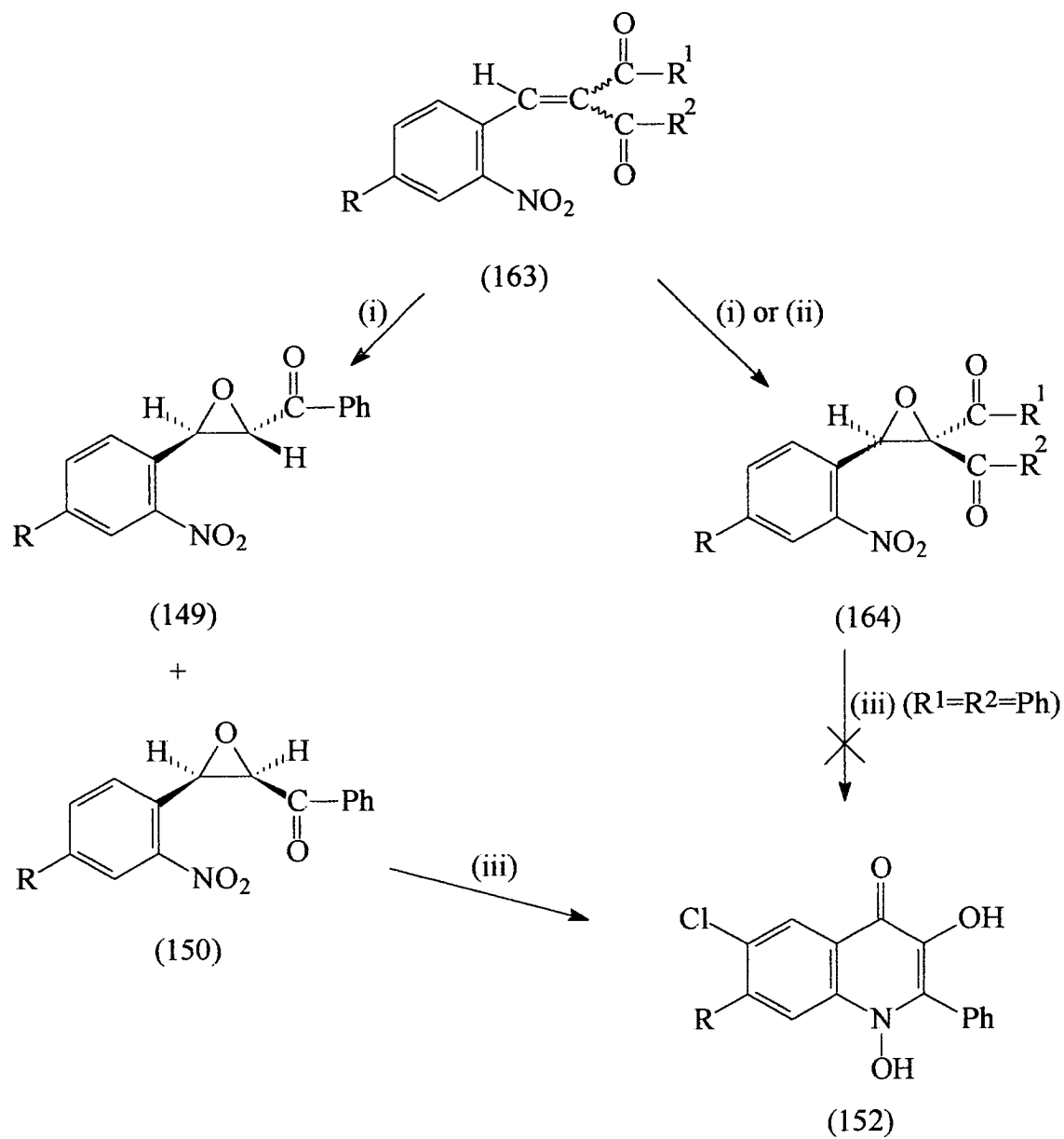
Scheme 33

derivative (156a). In practice though the N-oxide derivative (156a) was converted into the 3-hydroxyquinolinone derivative (158a) in high yield (82%) using sodium dithionite as the reducing agent. Further attempts (Scheme 33) were carried out to synthesise the 3,4-dioxoquinolinone derivative (156a). Triethyl phosphite is a widely used reagent⁷⁵ for the deoxygenation of heterocyclic N-oxides and in the present studies was not found to convert the N-oxide derivative (157a) into the 3,4-dioxoquinolinone derivative (156a). Instead the reaction gave a product in low yield (16%) whose combustion analysis and mass, IR, ¹H and ¹³C NMR spectra were consistent with the diethoxyquinoline derivative (162a). The formation of the diethoxyquinoline derivative (162a) is not very clear. The reaction may proceed by the initial deoxygenation of the N-oxide derivative (157a) to afford the 3,4-dioxoquinolinone derivative (156a) and subsequent reaction of the latter with triethyl phosphite gives a phosphorus complex (160a). The formation of the phosphorus complex (160a) is analogous to the reaction of trialkyl phosphites with aliphatic α -diketone derivatives⁷⁶. The phosphorus complex (160a) may then undergo alkyl group migration to afford the diethyl phosphonate derivative (161a). It is then proposed that the diethyl phosphonate derivative (161a) undergoes thermal rearrangement to the isolated diethoxyquinoline derivative (162a). Evidence to support the thermal rearrangement of the diethyl phosphonate (161a) to the diethoxyquinoline derivative (162a) is from the analogous thermolysis of phosphoranes to phosphonates⁷⁷. Further studies are necessary to firmly establish how the N-oxide (157a) is converted into the diethoxyquinoline derivative (162a) in the presence of triethyl phosphite.

A final attempt was made to obtain the 3,4-dioxoquinolinone derivative (156a). It was expected that the 3-hydroxyquinolinone derivative (158a) could be oxidised to the 3,4-dioxoquinolinone derivative (156a). However the oxidation of the 3-hydroxyquinolinone derivative (158a) using activated manganese dioxide as the catalyst gave the 3,4-dioxoquinolinone derivative (156a) in poor yield whose accurate mass, IR and ¹H NMR spectra were fully in accord with its structure. Very little of the 3,4-dioxoquinolinone derivative (156a) was isolated so its reaction with the dihydroxyquinolinone derivative (152a) could not be carried out. The reaction of

the 3,4-dioxoquinolinone derivative (156a) with the dihydroxyquinolinone derivative (152a) would have provided firm evidence for the mechanism outlined in Scheme 31. The simple (Scheme 32) chemical oxidation- reduction reactions which inter- relate the quinolinone derivatives [(152), (157), (158) and (156)] show how the dihydroxyquinolinone derivative (152a) may be regenerated in a biological system. As already discussed (see Chapter 1, section 2.2, page 5 and Scheme 4) it is important for drugs used to treat cancer to have a turnover capability similar to that exhibited by α -tocopherol. Most of the interconversions outlined in Scheme 32 have already been discussed. However the reduction of the N-oxide derivative (157a) to the dihydroxyquinolinone derivative (152a) was attempted to show that these N-oxide derivatives (157) could be easily converted back into the dihydroxyquinolinone derivatives (152) using chemical methods. It was found that the N-oxide derivative (157a) was smoothly transformed into the dihydroxyquinolinone derivative (152a) in high yield using hydrogen in the presence of palladium-on-charcoal.

As explained before (see Chapter 1, section 3.2, page 19 and Scheme 21) *trans* nitrophenyloxirane derivatives can be converted into the non- halogenated containing dihydroxyquinolinone derivatives by treatment with ethereal hydrogen chloride in the presence of hydroquinone. In the present studies however the hydrogen chloride catalysed cyclisation reaction of the *trans* nitrophenyloxirane derivative (149a) in the presence of hydroquinone afforded only the 1,2-diketone derivative (151a) in low yield. The *trans* nitrophenyloxirane derivative (149a) was of limited value since its acid- catalysed cyclisation reaction gave the dihydroxyquinolinone derivative (152a) in only moderate yield. As discussed before (see Chapter 1, section 3.2, page 19 and Scheme 21) *cis* nitrophenyloxirane derivatives react with hydrogen chloride to afford dihydroxyquinolinone derivatives in high yields. Therefore it would be advantageous to obtain *cis* nitrophenyloxirane derivatives as they are expected to cyclise to dihydroxyquinolinone derivatives in the presence of hydrogen chloride. The initial strategy (Scheme 29) was to convert the *trans* nitrophenyloxirane derivative (149a) into the *cis* nitrophenyloxirane derivative (150a). It is known⁷³ that *trans* 2-benzoyl-3-(2-nitrophenyl)oxirane can be converted into the corresponding *cis* nitrophenyloxirane derivative in the presence of methanolic sodium methoxide.

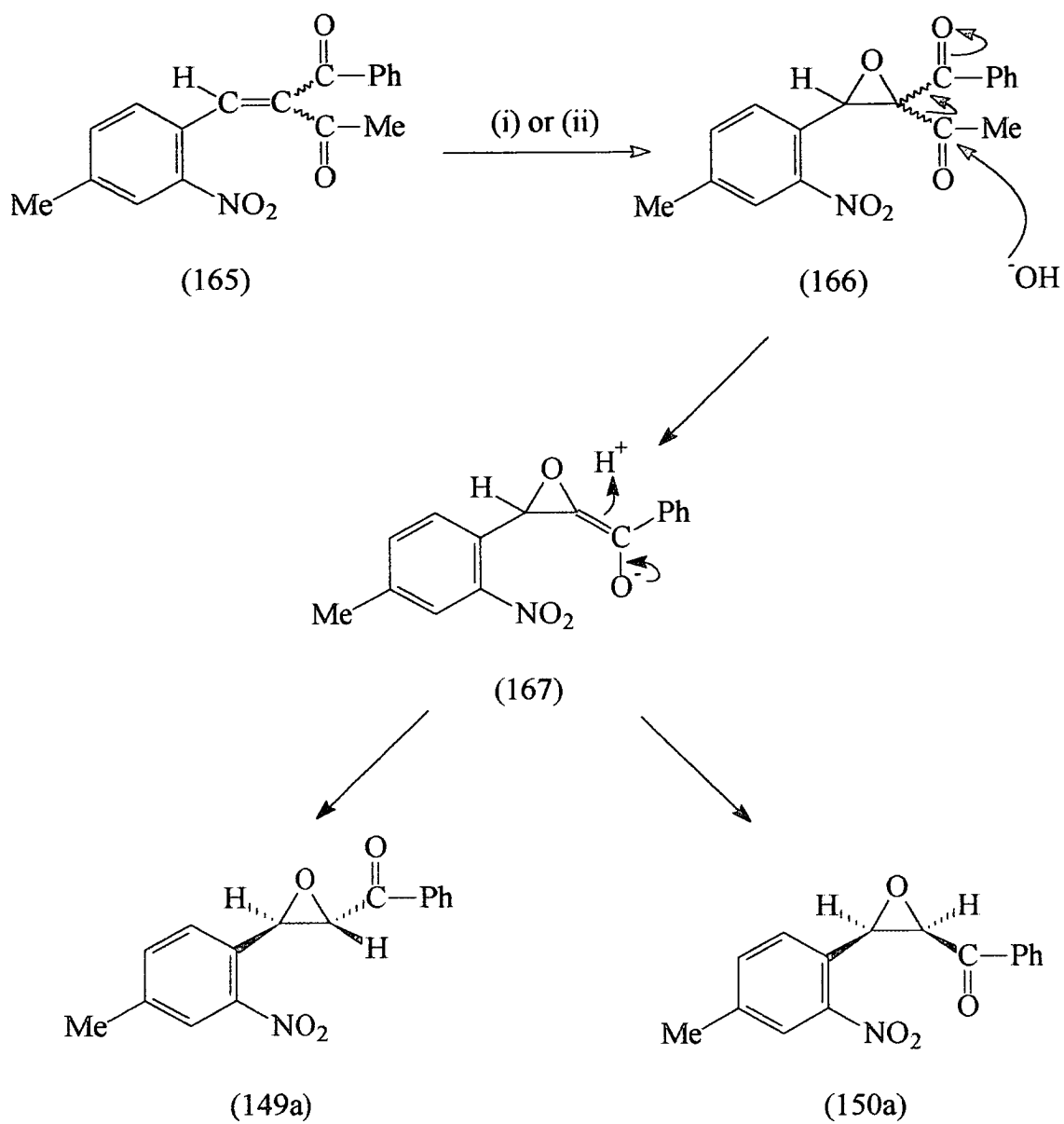


[R¹, R²=Me, Ph]

\underline{R}
 a; Me
 b; Cl
 c; NO₂

- (i) NaOCl (aqu.), dioxane or pyridine, room temp.
 (ii) NaOCl (aqu.), dioxane, 11°C.
 (iii) HCl_(g), DME, 0°C.

Scheme 34



(i) NaOCl (aqu.), dioxane or pyridine, room temp.

(ii) NaOCl (aqu.), dioxane, 11°C .

Scheme 35

Unfortunately the *trans* nitrophenyloxirane derivative (149a) failed to be transformed into the *cis* nitrophenyloxirane derivative (150a) in methanolic sodium methoxide. Only unreacted starting material was recovered from the reaction.

Attention was turned to synthesising other nitrophenyloxirane derivatives which contained a *cis* acyl group. The strategy (Scheme 34) involved converting the nitrobenzylidene derivatives (163) into the corresponding nitrophenyloxirane derivatives (164) which were hoped would cyclise to the dihydroxyquinolinone derivatives (152) in the presence of hydrogen chloride. It was found that the dibenzoyl substituted nitrobenzylidene derivative (163a; $R^1=R^2=Ph$) reacted with aqueous sodium hypochlorite solution in dioxane to afford the corresponding nitrophenyloxirane derivative (164a; $R^1=R^2=Ph$) in good yield (66%) whose combustion analysis and spectroscopic data were in agreement with its structure. The formation of the dibenzoyl substituted nitrophenyloxirane derivative (164a; $R^1=R^2=Ph$) prompted investigations on the synthesis of other *cis* acyl substituted nitrophenyloxirane derivatives (164). It was expected that the nitrobenzylidene derivative (163a; $R^1=Ph$; $R^2=Me$) would be converted into the methylnitrophenyloxirane derivative (164a; $R^1=Ph$; $R^2=Me$) using aqueous sodium hypochlorite solution. In fact the nitrobenzylidene derivative (163a; $R^1=Ph$; $R^2=Me$) reacted with aqueous sodium hypochlorite solution to afford the *trans* nitrophenyloxirane derivative (149a) in low yield (12%) and the *cis* nitrophenyloxirane derivative (150a) in moderate yield (55%). The *cis* nitrophenyloxirane derivative (150a) analysed correctly and had spectroscopic properties consistent with its structure. Significantly the 1H NMR spectrum of the *cis* nitrophenyloxirane derivative (150a) shows oxirane ring protons with coupling constants ($J_{5.1}$) attributable⁷⁸ to a *cis* configuration. Previous studies⁷³ had explained that the preferential formation of the *cis* nitrophenyloxirane derivative was due to the *cis* isomer being less soluble than the *trans* isomer. However this explanation is not valid in the present studies. It is proposed (Scheme 35) that the methylnitrobenzylidene derivative (165) is initially converted into the corresponding methylnitrophenyloxirane derivative (166) in the presence of aqueous sodium hypochlorite solution. The methylnitrophenyloxirane derivative (166) then undergoes a retro- Claisen type reaction with the loss of glacial acetic acid promoted by the

small quantity of hydroxy anions present in the reaction mixture to give the enolate intermediate (167). It is not understood why the *cis* nitrophenyloxirane derivative (150a) is formed preferentially over the *trans* nitrophenyloxirane derivative (149a) when the enolate intermediate (167) picks up a proton. Further detailed studies on this reaction are necessary to understand how the reaction proceeds.

The synthesis of the *cis* nitrophenyloxirane derivative (150a) allowed studies on the behaviour of this derivative to undergo acid- catalysed cyclisation to the dihydroxyquinolinone derivative (152a). It was expected (Scheme 34) that the *cis* nitrophenyloxirane derivative (150a) would react more readily than the *trans* isomer (149a) with hydrogen chloride to give the dihydroxyquinolinone derivative (152a). As anticipated the hydrogen chloride catalysed reaction of the *cis* nitrophenyloxirane derivative (150a) in dimethoxyethane gave the dihydroxyquinolinone derivative (152a) in excellent yield (86%).

In parallel to work already discussed investigations were carried out on the chloronitrophenyloxirane derivative (149b) with regard to its conversion into the dihydroxyquinolinone derivative (152b) in the presence of hydrogen chloride. The chloro substituent in the chloronitrophenyloxirane derivative (149b) is a good example of an electron withdrawing group. It was anticipated that the electron withdrawing effect of the chloro substituent in the nitrophenyloxirane derivative (149b) would increase the electrophilicity of the side- chain and this might therefore promote the adjacent nitro group to react readily with the side- chain in the presence of hydrogen chloride to give the dihydroxyquinolinone derivative (152b). The same strategy (Scheme 29) was utilised as for synthesising the *trans* methylnitrophenyloxirane derivative (149a). 4-Chloro-2-nitrobenzaldehyde (135b) reacted with 2-bromoacetophenone (148) in methanolic sodium methoxide to afford a product in excellent yield (78%) identified on the basis of its combustion analysis and mass, IR and ¹H NMR spectra as the required *trans* nitrophenyloxirane derivative (149b).

Initially (Scheme 30) the reaction of the *trans* nitrophenyloxirane derivative (149b) with hydrogen chloride was investigated in the hope that the dihydroxyquinolinone

derivative (152b) would be isolated in high yield. Unfortunately the hydrogen chloride catalysed cyclisation reaction of the *trans* nitrophenyloxirane derivative (149b) in dioxane gave three products each in poor yield. The main product had combustion analysis and spectroscopic properties to support its formulation as the dihydroxyquinolinone derivative (152b). A diketone derivative (151b) was also isolated from the reaction of the nitrophenyloxirane derivative (149b) with hydrogen chloride whose combustion analysis and spectroscopic data were fully in accord with its structure. As with the methyl 1,2-diketone derivative (151a), the chloro 1,2-diketone derivative (151b) showed a high carbonyl band at 1715cm^{-1} in its IR spectrum which supports the 1,2-diketone structure (151b) and not the isomeric 1-phenyl-3-(4-chloro-2-nitrophenyl)propane-1,3-dione structure. Rearrangement of the oxirane ring in the nitrophenyloxirane derivative (149b) accounts for the formation of the 1,2-diketone derivative (151b). The third product from the reaction of the nitrophenyloxirane derivative (149b) with hydrogen chloride was the chlorohydrin derivative (153b) whose combustion analysis and mass, IR and ^1H NMR spectra were in agreement with its assigned structure. The formation of the chlorohydrin derivative (153b) involves the orthodox⁷⁴ reaction of hydrogen chloride with the oxirane ring in the nitrophenyloxirane derivative (149b).

An attempt was made to confirm the dihydroxyquinolinone structure (152b) by reaction of the dihydroxyquinolinone derivative (152b) with acetic anhydride. It was originally thought that the dihydroxyquinolinone derivative (152b) would react with acetic anhydride to form the N-acetoxy derivative (154b). In fact the dichloro substituted dihydroxyquinolinone derivative (152b) reacted with acetic anhydride in a similar way to when the methyl substituted dihydroxyquinolinone derivative (152a) was subjected to the same reaction conditions. Heating (Scheme 31) the dichloro dihydroxyquinolinone derivative (152b) under reflux in acetic anhydride gave the 3-acetoxy derivative (159b) in low yield whose accurate mass, IR and ^1H NMR spectra were in support of its structure. In particular the 3-acetoxy derivative (159b) had an IR absorption at 1769cm^{-1} attributed to the carbonyl in the acetoxy group. It was interesting to know how the dihydroxyquinolinone derivative (152b) would react with acetic anhydride under milder conditions. Previously the methyl dihydroxyquinolinone derivative (152a) reacted with acetic anhydride at 100°C to

give a mixture of the 3-acetoxy derivative (159a) and the N-oxide derivative (157a). In fact treating the dichloro dihydroxyquinolinone derivative (152b) with acetic anhydride at 100°C gave a red solid tentatively assigned as a mixture of the 3-acetoxy and N-oxide derivatives (159b) and (157b). The mixture was assigned based upon the comparison of its ^1H NMR spectrum with the ^1H NMR spectrum of the solid obtained from the analogous reaction of the methyl dihydroxyquinolinone derivative (152a) with acetic anhydride.

Evidence was sought to prove the synthesis of the N-oxide derivative (157b) in the reaction of the dihydroxyquinolinone derivative (152b) with acetic anhydride. As expected (Scheme 32) the dihydroxyquinolinone derivative (152b) was converted into the N-oxide derivative (157b) in good yield using manganese dioxide as the oxidising agent. The N-oxide derivative (157b) analysed correctly and had spectroscopic properties consistent with its structure. Support for the formation of the dihydroxyquinolinone derivative (152b) was provided by its reduction to the 3-hydroxyquinolinone derivative (158b). Heating the dihydroxyquinolinone derivative (152b) with sodium dithionite under reflux in aqueous ethanol afforded the 3-hydroxyquinolinone derivative (158b) in high yield (87%) whose combustion analysis and spectroscopic properties were in agreement with its structure.

Investigations were carried out on the reaction of the dihydroxyquinolinone derivative (152b) with tosyl chloride. It was thought the dihydroxyquinolinone derivative (152b) would react with tosyl chloride, in a similar way to the reaction of the methyl dihydroxyquinolinone derivative (152a) with tosyl chloride, and afford a mixture of the N-oxide and 3-hydroxyquinolinone derivatives (157b) and (158b). In practice the reaction of the dihydroxyquinolinone derivative (152b) with tosyl chloride in the presence of triethylamine gave as expected the N-oxide and 3-hydroxyquinolinone derivatives (157b) and (158b) each in low yields. The reaction of the dihydroxyquinolinone derivative (152b) with tosyl chloride is thought to proceed via the 3,4-dioxoquinolinone derivative (156b) which reacts with unreacted dihydroxyquinolinone derivative (152b) to afford the N-oxide and

3-hydroxyquinolinone derivatives (157b) and (158b). Attempts were carried out to obtain the 3,4-dioxoquinolinone derivative (156b) and therefore provide evidence for the mechanism outlined in Scheme 31. An initial attempt to obtain the 3,4-dioxoquinolinone derivative (156b) involved the reduction of the N-oxide derivative (157b). However heating the N-oxide derivative (157b) with sodium dithionite under reflux in aqueous ethanol gave only the 3-hydroxyquinolinone derivative (158b) in high yield. It was proposed that concentrated sulfuric acid could be used as a dehydrating agent and promote the conversion of the dihydroxyquinolinone derivative (152b) into the 3,4-dioxoquinolinone derivative (156b). Unfortunately the dihydroxyquinolinone derivative (152b) failed to react with concentrated sulfuric acid.

Further routes to synthesising the 3,4-dioxoquinolinone derivative (156b) were investigated. Triethylphosphite is a reagent that can be used to deoxygenate N-oxygenated heterocyclic compounds. However heating the N-oxide (157b) with triethyl phosphite under reflux failed to afford the 3,4-dioxoquinolinone derivative (156b). Instead the reaction involving triethyl phosphite gave a product in low yield (37%) whose combustion analysis and mass, IR, ^1H and ^{13}C NMR spectra supported its formulation as the diethoxyquinoline derivative (162b). As discussed earlier the methyl dihydroxyquinolinone derivative (152a) also reacted with triethyl phosphite to give a diethoxyquinolinone derivative (162a). A final attempt was made to obtain the 3,4-dioxoquinolinone derivative (156b). The 3-hydroxyquinolinone derivative (158b) should be easily oxidised to the corresponding 3,4-dioxoquinolinone derivative (156b). In fact the 3-hydroxyquinolinone derivative (158b) was transformed into the 3,4-dioxoquinolinone derivative (156b) in poor yield using manganese dioxide as the oxidising agent. The 3,4-dioxoquinolinone derivative (156b) was tentatively assigned on the basis of combustion analysis, IR and ^1H NMR spectra. Unfortunately the mass spectrum of the 3,4-dioxoquinolinone derivative (156b) showed no molecular ion at m/z 304 (or isotope peaks) which would correspond to the 3,4-dioxoquinolinone derivative (156b).

As discussed in the introductory chapter (see Chapter 1, section 2.2, page 5 and Scheme 4) it would be useful to synthesise dihydroxyquinolinone derivatives

because of their biological properties. In particular (Scheme 32) dihydroxyquinolinone derivatives have the potential to be effective anti-cancer agents. Dihydroxyquinolinone derivatives (152) are inter-related with other quinolinone derivatives [(152) \rightleftharpoons (157) \rightleftharpoons (156) \rightleftharpoons (158)]. These simple oxidation-reduction reactions offer the possibility of the dihydroxyquinolinone derivative (152b) being easily regenerated, which is particularly useful in a biological system. An attempt was made to chemically regenerate the dihydroxyquinolinone derivative (152b) from the corresponding N-oxide derivative (157b). If the regeneration of the dihydroxyquinolinone derivative (152b) can occur readily in a chemical environment it may also occur in a biological environment. It was found that hydrogenating the N-oxide derivative (157b) in the presence of palladium-on-charcoal afforded the dihydroxyquinolinone derivative (152b) in excellent yield (94%).

Attention was next turned to synthesising (Scheme 29) the *cis* nitrophenyloxirane derivative (150b). It was expected that the *cis* nitrophenyloxirane derivative (150b) would react with hydrogen chloride to give the dihydroxyquinolinone derivative (152b) in high yield. The initial attempt to obtain the *cis* nitrophenyloxirane derivative (150b) was to epimerise the *trans* nitrophenyloxirane derivative (149b). In practice however the *trans* nitrophenyloxirane derivative (149b) failed to be converted into the *cis* nitrophenyloxirane derivative (150b) in methanolic sodium methoxide. Studies were carried out on synthesising nitrophenyloxirane derivatives which contained a *cis* acyl group. It has already been shown how methylnitrobenzylidene derivatives (163a) can be transformed into the methylnitrophenyloxirane derivatives (164a) with aqueous sodium hypochlorite solution. A similar strategy (Scheme 34) was used for the chloronitrobenzylidene derivatives (163b) with regard to obtaining the diacyl substituted nitrophenyloxirane derivatives (164b). These nitrophenyloxirane derivatives (164b; R¹=Me or Ph; R²=Ph) were expected to cyclise to the dihydroxyquinolinone derivative (152b) in the presence of hydrogen chloride. It was found that the chloronitrobenzylidene derivative (163b; R¹=Ph; R²=Ph) reacted with aqueous sodium hypochlorite solution in pyridine to afford the corresponding dibenzoyl substituted nitrophenyloxirane derivative (164b; R¹=Ph; R²=Ph) in poor yield which analysed correctly and had spectroscopic data in accord with its structure. Repeating the reaction of the

nitrobenzylidene derivative (163b; $R^1=Ph$; $R^2=Ph$) with aqueous sodium hypochlorite solution in dioxane instead of pyridine gave the nitrophenyloxirane derivative (164b; $R^1=Ph$; $R^2=Ph$) in moderate yield (49%).

Further studies were carried out to ascertain whether the nitrophenyloxirane derivative (164b; $R^1=Ph$; $R^2=Ph$) could be obtained in higher yield. Treating the nitrobenzylidene derivative (163b; $R^1=Ph$; $R^2=Ph$) with aqueous sodium hypochlorite solution at a low temperature also gave the nitrophenyloxirane derivative (164b; $R^1=Ph$; $R^2=Ph$) in poor yield. A final attempt was made to synthesise the nitrophenyloxirane derivative (164b; $R^1=Ph$; $R^2=Ph$) in improved yield. Treatment of the nitrobenzylidene derivative (163b; $R^1=Ph$; $R^2=Ph$) with aqueous sodium hypochlorite solution over a prolonged reaction time afforded the nitrophenyloxirane derivative (164b; $R^1=Ph$; $R^2=Ph$) in only moderate yield. The reaction of the nitrophenyloxirane derivative (164b; $R^1=Ph$; $R^2=Ph$) with hydrogen chloride was carried out in the hope of forming the dihydroxyquinolinone derivative (152b) in high yield. Disappointingly though the reaction of hydrogen chloride with the nitrophenyloxirane derivative (164b; $R^1=Ph$; $R^2=Ph$) in dimethoxyethane gave only an intractable gum.

An attempt was made to extend this work to synthesising the diacetyl substituted nitrophenyloxirane derivative (164b; $R^1=Me$; $R^2=Me$) as this derivative was expected to cyclise in the presence of hydrogen chloride to 6,7-dichloro-1,4-dihydro-1,3-dihydroxy-2-methyl-4-oxoquinoline. Unfortunately the nitrophenyloxirane derivative (163b; $R^1=Me$; $R^2=Me$) reacted with aqueous sodium hypochlorite solution in dioxane to give only a small quantity of an intractable oil. It has been shown that the 4-methylnitrobenzylidene derivative (163a; $R^1=Ph$; $R^2=Me$) reacts with aqueous sodium hypochlorite solution to afford the *cis* and *trans* nitrophenyloxirane derivatives (150a) and (149a). This method was utilised with the chloronitrobenzylidene derivative (163b; $R^1=Ph$; $R^2=Me$) to obtain the *cis* nitrophenyloxirane derivative (150b). It was expected that the *cis* nitrophenyloxirane derivative (150b) would react with hydrogen chloride to give the dihydroxyquinolinone derivative (152b) in high yield. In practice the chloronitrobenzylidene derivative (163b; $R^1=Ph$; $R^2=Me$) was converted into the *cis*

nitrophenyloxirane derivative (150b) (yield 52%) and the *trans* nitrophenyloxirane derivative (149b) (yield 12%) in the presence of aqueous sodium hypochlorite solution. The *cis* nitrophenyloxirane derivative (150b) had combustion analysis and spectroscopic properties consistent with its structure. Significantly the ^1H NMR spectrum of the *cis* nitrophenyloxirane derivative (150b) showed oxirane ring proton coupling constants ($J_{5,1}$) attributable to a *cis* configuration. Notably the *cis* nitrophenyloxirane derivative (150b) reacted with hydrogen chloride to afford the dihydroxyquinolinone derivative (152b) in excellent yield (93%). In comparison with this reaction the hydrogen chloride catalysed cyclisation of the *trans* nitrophenyloxirane derivative (149b) gave only a low yield of the dihydroxyquinolinone derivative (152b).

Attention was next turned to investigating (Scheme 30) the 4-nitro substituted nitrophenyloxirane derivative (149c) with regard to its acid- catalysed cyclisation reaction to the dihydroxyquinolinone derivative (152c). The nitro group para to the side- chain in the nitrophenyloxirane derivative (149c) is strongly electron withdrawing and so may enhance the electrophilicity of the side- chain. The effect of the 4-nitro group in the nitrophenyloxirane derivative (149c) may therefore lead to improved cyclisation of the nitrophenyloxirane derivative (149c) to the dihydroxyquinolinone derivative (152c) in the presence of hydrogen chloride. The initial strategy (Scheme 34) was to obtain the *trans* nitrophenyloxirane derivative (149c). In comparison with the methyl and chloro nitrobenzylidene derivatives (163a; $\text{R}^1=\text{Ph}$; $\text{R}^2=\text{Me}$) and (163b; $\text{R}^1=\text{Ph}$; $\text{R}^2=\text{Me}$), the dinitrobenzylidene derivative (160c; $\text{R}^1=\text{Ph}$; $\text{R}^2=\text{Me}$) was transformed into a separable mixture of the *cis* and *trans* nitrophenyloxirane derivatives (149c) and (150c) each in moderate yields in the presence of aqueous sodium hypochlorite solution. Both the *cis* and *trans* nitrophenyloxirane derivatives (149c) and (150c) analysed correctly and had spectroscopic data in accord with their assigned structures.

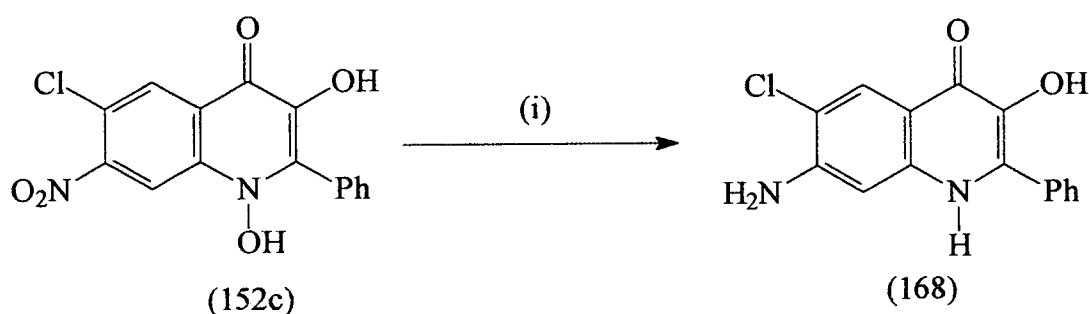
In parallel to work already discussed investigations (Scheme 30) were carried out on the acid- catalysed cyclisation of the *trans* nitrophenyloxirane derivative (149c) to the dihydroxyquinolinone derivative (152c). In comparison with the methyl and chloro nitrophenyloxirane derivatives (149a and b), the hydrogen chloride catalysed

cyclisation reaction of the *trans* nitrophenyloxirane derivative (149c) to the dihydroxyquinolinone derivative (152c) failed and gave unreacted starting material as the only identifiable material. Studies were then carried out on the reaction (Scheme 34) of the *cis* nitrophenyloxirane derivative (150c) with hydrogen chloride in the hope of forming the dihydroxyquinolinone derivative (152c). In comparison with the *trans* nitrophenyloxirane derivative (149c), the *cis* nitrophenyloxirane derivative (150c) did react with hydrogen chloride in dimethoxyethane to afford the dihydroxyquinolinone derivative (152c) in high yield (73%). The dihydroxyquinolinone derivative (152c) had combustion analysis and spectroscopic properties in agreement with its structure. Repeating the hydrogen chloride catalysed reaction of the *cis* nitrophenyloxirane derivative (150c) over a longer reaction time failed to give the dihydroxyquinolinone derivative (152c) in an improved yield.

Formation (Scheme 30) of a simple N-acetoxy derivative would confirm the dihydroxyquinolinone structure (152c). Unfortunately the dihydroxyquinolinone derivative (152c) failed to be converted into the acetoxy derivative (154c) using acetyl chloride in the presence of triethylamine. Instead (Scheme 31) the reaction produced the N-oxide and the 3-acetoxy derivatives (157c) and (159c) each in low yields, which is a result similar to those obtained from the reactions discussed earlier of the dichloro and methyl dihydroxyquinolinone derivatives (152a and b) with acetic anhydride. The N-oxide (157c) analysed correctly and had spectroscopic properties in agreement with its structure. The 3-acetoxy derivative (159c) was assigned on the basis of its accurate mass and IR spectrum. Insufficient material of the 3-acetoxy derivative (159c) was isolated to obtain a ^1H NMR spectrum of the derivative. Carrying out the reaction of the dihydroxyquinolinone derivative (152c) with excess acetyl chloride in the presence of triethylamine failed to give the 3-acetoxy derivative (159c) in improved yield. This reaction only afforded the N-oxide derivative (157c) in poor yield. The reaction of the dihydroxyquinolinone derivative (152c) with acetic anhydride at 100°C also failed to give the N-acetoxy derivative (154c). Instead the reaction afforded an inseparable red mixture of the 3-acetoxy derivative (159c) and the N-oxide derivative (157c), tentatively based upon comparison of its IR and ^1H NMR spectra with the authentic IR and ^1H NMR spectra obtained from the N-oxide and 3-acetoxy derivatives (157c) and (159c).

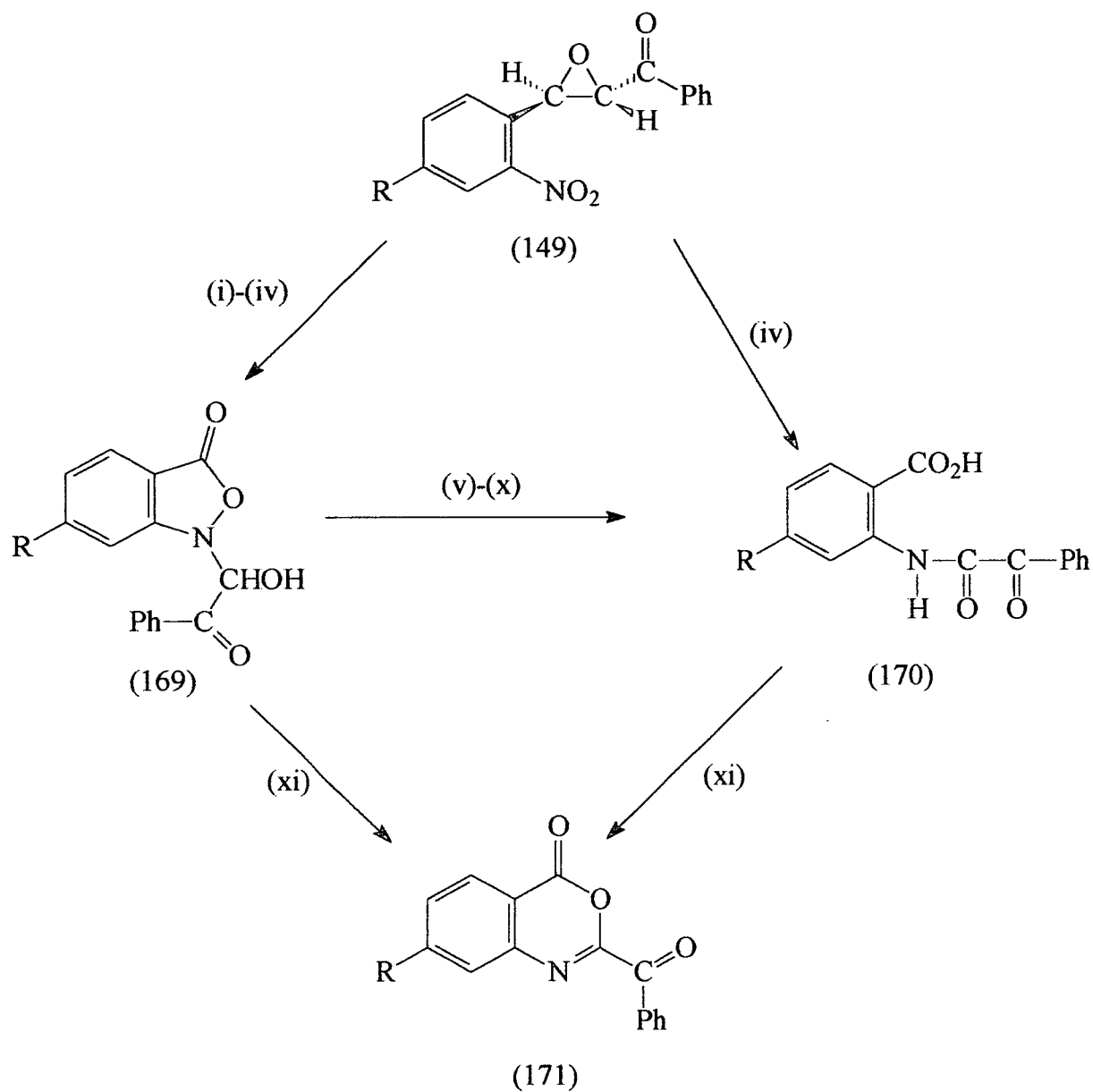
Evidence (Scheme 32) for the N-oxide (157c) was provided by its synthesis from oxidation of the parent dihydroxyquinolinone derivative (152c). The dihydroxyquinolinone derivative (152c) was smoothly converted into the corresponding N-oxide (157c) in high yield using activated manganese dioxide in dimethylformamide.

An attempt was made to reduce the dihydroxyquinolinone derivative (152c) to the 3-hydroxyquinolinone derivative (158c) and so confirm its structure. However heating the dihydroxyquinolinone derivative (152c) with sodium dithionite under reflux in aqueous ethanol failed to afford the 3-hydroxyquinolinone derivative (158c). Instead (Scheme 36) this reaction gave a product in high yield (82%) whose accurate mass, IR and ^1H NMR spectra allow its formulation as the 7-amino-3-hydroxyquinolinone derivative (168). Further attempts were made to reduce the dihydroxyquinolinone derivative (152c) to the 3-hydroxyquinolinone derivative (158c). It was found that hydrogenating the dihydroxyquinolinone derivative (152c) in ethanol using palladium-on-charcoal as the catalyst gave only an intractable solid. Unfortunately changing the solvent in the hydrogenation reaction to glacial acetic acid also afforded an intractable solid.



(i) $\text{Na}_2\text{S}_2\text{O}_4$, EtOH, H_2O , reflux.

Scheme 36



R
a; Me
b; Cl
c; NO₂

- (i) AlCl₃, DCM, -10°C.
(ii) SnCl₄, toluene or DCM, room temp.
(iii) BCl₃, DCM, -10°C.
(iv) BF₃.Et₂O, DME, reflux.
(v) 2M NaOH, heat.
(vi) H₂, catalyst, dioxane or AcOH, atmos. press.

- (vii) MnO₂, DME, room temp.
(viii) NaOEt, EtOH, reflux.
(ix) silicagel, DCM, room temp.
(x) BF₃.Et₂O, DME, room temp.
(xi) Ac₂O, reflux.

Scheme 37

4. STUDIES ON THE SCOPE OF THE LEWIS ACID CATALYSED CYCLISATION REACTIONS OF 2-NITROPHENYLOXIRANE DERIVATIVES TO 2,1-BENZISOXAZOLES AND RELATED COMPOUNDS

As discussed in Chapter 1 (see Chapter 1, section 3.1, page 15 and Scheme 13) previous studies in this area have shown that nitrophenyloxirane derivatives are converted into 2,1-benzisoxazolone derivatives or 2-aminobenzoic acid derivatives using Lewis acids as catalysts. The proposed mechanism (see Chapter 1, section 3.1, page 16 and Scheme 14) of formation of the 2,1-benzisoxazolone derivatives or 2-aminobenzoic acid derivatives from the nitrophenyloxirane derivatives occurs via a nitroso intermediate similar to the nitroso intermediate proposed (see Chapter 1, section 3.2, page 19 and Scheme 21) in the hydrogen chloride catalysed cyclisation reactions of nitrophenyloxirane derivatives to dihydroxyquinolinone derivatives. Studies were carried out on investigating (Scheme 37) the acid- catalysed cyclisation reactions of substituted nitrophenyloxirane derivatives (149a-c) to 2,1-benzisoxazolone derivatives (169a-c). In particular attention was paid to the effects of an electron withdrawing or electron donating group para to the side- chain in the nitrophenyloxirane derivative (149a-c) when the nitrophenyloxirane derivative (149a-c) reacted in the presence of a Lewis acid to afford a 2,1-benzisoxazolone derivative (169a-c).

Initially investigations were carried out on the electron donating effects of a methyl group para to the side- chain in a nitrophenyloxirane derivative (149a) with regard to the nitrophenyloxirane derivative (149a) reacting in the presence of a Lewis acid to give a 2,1-benzisoxazolone derivative (169a). It was thought that the methyl group would donate electrons into the benzene ring and consequently a reduction would occur in the electrophilicity of the para side- chain. As a result the nitro group adjacent to the side- chain in the nitrophenyloxirane derivative (149a) may not readily react with the side- chain in the presence of a lewis acid to give the 2,1-benzisoxazolone derivative (169a). However it was found that the nitrophenyloxirane derivative (149a) reacted in toluene in the presence of stannic chloride to afford a product in high yield (87%) whose combustion analysis and mass, IR and ¹H NMR spectra allowed its formulation as the 2,1-benzisoxazolone

derivative (169a). The 2,1-benzisoxazolone derivatives are known⁵⁰ to be converted into benzoxazine derivatives using acetic anhydride. Evidence for the 2,1-benzisoxazolone derivative (169a) was provided by its conversion into the benzoxazine derivative (171a). Heating the 2,1-benzisoxazolone derivative (169a) under reflux with acetic anhydride gave a product in moderate yield (38%) which analysed correctly and had spectroscopic properties consistent with the benzoxazine structure (171a). In particular the IR spectrum of the benzoxazine derivative (171a) had absorptions at 1753 and 1667cm⁻¹ attributed to the carbonyl groups in this derivative.

Further evidence was sought for the 2,1-benzisoxazolone derivative (169a). Previous work⁵⁰ had shown that 2,1-benzisoxazolone derivatives may be transformed into 2-aminobenzoic acid derivatives. The initial attempt to convert the 2,1-benzisoxazolone derivative (169a) into the 2-aminobenzoic acid derivative (170a) failed, when heating the former derivative in 2M aqueous sodium hydroxide solution. This reaction gave only an intractable red oil. Other methods were investigated of converting the 2,1-benzisoxazolone derivative (169a) into the 2-aminobenzoic acid derivative (170a) in the anticipation of obtaining further evidence for the correct structural assignment of the 2,1-benzisoxazolone derivative (169a). Attempts were made to reductively cleave open the isoxazole ring of the 2,1-benzisoxazolone derivative (169a) so as to produce the 2-aminobenzoic acid derivative (170a). Hydrogenation of the 2,1-benzisoxazolone derivative (169a) using palladium-on-charcoal as the catalyst in dioxane gave unreacted starting material as the only identifiable material. Repeating the hydrogenation reaction in glacial acetic acid instead of dioxane also failed to afford the 2-aminobenzoic acid derivative (170a). Instead the reaction gave an intractable solid. Similarly the 2,1-benzisoxazolone derivative (169a) was not converted into the 2-aminobenzoic acid derivative (170a) when the former was hydrogenated using Raney nickel as the catalyst.

Other ways of transforming the 2,1-benzisoxazolone derivative (169a) into the 2-aminobenzoic acid derivative (170a) were investigated with the expectation of confirming the structure of the 2,1-benzisoxazolone derivative (169a). It was found that the 2,1-benzisoxazolone derivative (169a) could not be converted into the 2-aminobenzoic acid derivative (170a) in the presence of sodium borohydride. Only an intractable solid was produced in the reaction. It was expected that the isoxazole ring of the 2,1-benzisoxazolone derivative (169a) would open under basic conditions to give the 2-aminobenzoic acid derivative (170a). However heating the 2,1-benzisoxazolone derivative (169a) with sodium ethoxide under reflux in ethanol afforded only an intractable brown solid. Confirmatory proof of the 2,1-benzisoxazolone derivative (169a) was sought by its oxidation to 1-N-(1-benzoyl-1-oxo)methyl-1,3-dihydro-6-methyl-3-oxo-2,1-benzisoxazole. It was interesting to discover that the 2,1-benzisoxazolone derivative (169a) reacted with manganese dioxide in dimethoxyethane to afford instead the 2-aminobenzoic acid derivative (170a) in poor yield which analysed correctly and showed spectroscopic properties consistent with its structure. The mechanism by which this reaction occurs is not understood and requires further detailed investigation.

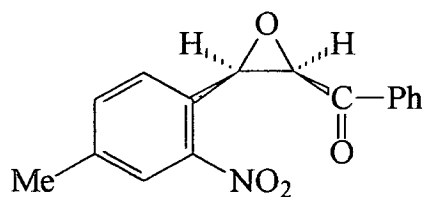
Investigations were carried out on solvent effects in the Lewis acid catalysed cyclisation reaction of the nitrophenyloxirane derivative (149a) to the 2,1-benzisoxazolone derivative (169a). In fact the *trans* nitrophenyloxirane derivative (149a) was transformed into the 2,1-benzisoxazolone derivative (169a) in poor yield in the presence of stannic chloride in dichloromethane (instead of toluene). Studies were also carried out on the Lewis acid catalysed cyclisation reaction of the *cis* nitrophenyloxirane derivative (150a) to the 2,1-benzisoxazolone derivative (169a) to see if the *cis* acyl group had a significant effect in the cyclisation process. In contrast with the *trans* nitrophenyloxirane derivative (149a), the *cis* nitrophenyloxirane derivative (150a) reacted with stannic chloride to afford both the 2,1-benzisoxazolone derivative (169a) and the 2-aminobenzoic acid derivative (170a) each in moderate yields.

As discussed in the introductory Chapter (section 3.1, page 15 and Scheme 13), boron trifluoride had been utilised to convert nitrophenyloxirane derivatives into

2-aminobenzoic acid derivatives. It was expected that boron trifluoride would transform the nitrophenyloxirane derivative (149a) into the 2-aminobenzoic acid derivative (170a). As anticipated heating the *trans* nitrophenyloxirane derivative (149a) with boron trifluoride etherate under reflux in dimethoxyethane afforded the 2-aminobenzoic acid derivative (170a) in moderate yield (52%). Further evidence for the formation of the 2-aminobenzoic acid derivative (170a) was provided by its reaction with acetic anhydride. Heating the 2-aminobenzoic acid derivative (170a) under reflux in acetic anhydride gave the expected benzoxazine derivative (171a) in good yield. It was thought that the 2,1-benzisoxazolone derivative (169a) may undergo acid catalysed rearrangement to the 2-aminobenzoic acid derivative (170a). Unfortunately this was not the case as treating the 2,1-benzisoxazolone derivative (169a) with silicagel in dichloromethane resulted in no reaction.

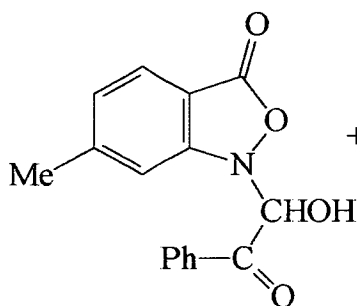
Studies were carried out on the effect of treating the 2,1-benzisoxazolone derivative (169a) with boron trifluoride etherate. It is already known⁵⁰ that nitrophenyloxirane derivatives are transformed into the 2-aminobenzoic acid derivatives in the presence of boron trifluoride etherate. It was therefore anticipated that the 2,1-benzisoxazolone derivative (169a) might rearrange into the 2-aminobenzoic acid derivative (170a) in the presence of boron trifluoride. In practice boron trifluoride catalysed the conversion of the 2,1-benzisoxazolone derivative (169a) into the corresponding 2-aminobenzoic acid derivative (170a) in dimethoxyethane in good yield (67%).

Attention was next turned to studying the effect of a *cis* acyl group present in the nitrophenyloxirane derivative (150a) with regard to its reaction with boron trifluoride etherate. It was hoped that the *cis* acyl group of the nitrophenyloxirane derivative (150a) would cause the nitro group to react readily with the ortho- side- chain and as a result the 2-aminobenzoic acid derivative (170a) would be obtained in improved yield. In comparison with the *trans* nitrophenyloxirane derivative (149a), the *cis* nitrophenyloxirane derivative (150a) reacted with boron trifluoride etherate in dimethoxyethane to afford the 2,1-benzisoxazolone derivative (169a) in low yield (9%) and the 2-aminobenzoic acid derivative (170a) in high yield (71%).



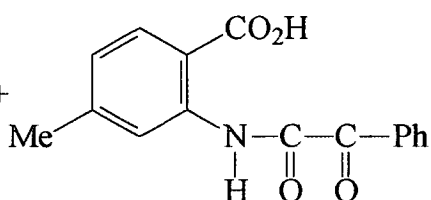
(150)

(i) or (ii)

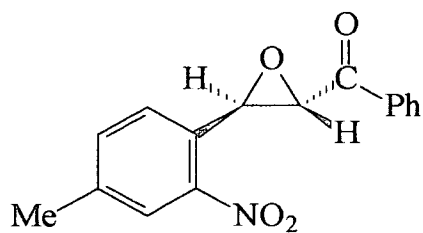


(169a)

+

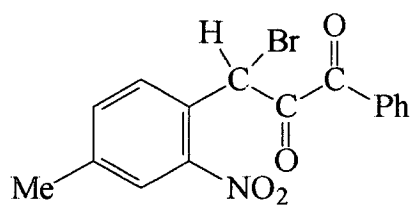


(170a)



(149a)

(iii)



(172)

(i) SnCl_4 , DCM, room temp.

(ii) $\text{BF}_3 \cdot \text{Et}_2\text{O}$, DME, reflux.

(iii) BBr_3 , DCM, -10°C .

Scheme 38

The acid- catalysed cyclisation reaction of the nitrophenyloxirane derivative (149a) to the 2,1-benzisoxazolone derivative (169a) was investigated with other Lewis acids. The *trans* nitrophenyloxirane derivative (149a) failed to be converted into the 2,1-benzisoxazolone derivative (169a) using aluminium chloride as the catalyst. Instead this reaction afforded only an intractable brown solid. Studies (Scheme 38) were undertaken on the effect of using the related Lewis acids to boron trifluoride, namely boron trichloride and boron tribromide, in the acid catalysed cyclisation reaction of the nitrophenyloxirane derivative (149a) to the 2,1-benzisoxazolone derivative (169a). It was interesting to know if these related Lewis acids to boron trifluoride would promote the cyclisation of the nitrophenyloxirane derivative (149a) to the 2,1-benzisoxazolone derivative (169a). Unfortunately treating the *trans* nitrophenyloxirane derivative (149a) with boron trichloride in dichloromethane afforded unreacted starting material as the only identifiable material. Similarly the boron tribromide catalysed cyclisation reaction of the nitrophenyloxirane derivative (149a) failed to give the 2,1-benzisoxazolone derivative (169a). Instead the reaction afforded a product in low yield (18%) whose combustion analysis and spectroscopic properties allow its formulation as the bromo 1,2-diketone derivative (172). The Lewis acid catalysed rearrangement of the nitrophenyloxirane derivative (149a) followed by bromination accounts for the formation of the bromo 1,2-diketone derivative (172).

In parallel to the work carried out on the methylnitrophenyloxirane derivative (149a), studies (Scheme 37) were undertaken on the lewis acid catalysed cyclisation reaction of the chloronitrophenyloxirane derivative (149b) to the 1,2-benzisoxazolone derivative (169b). The chloro substituent in the nitrophenyloxirane derivative (149b) is electron withdrawing so may have the opposite effect to a methyl substituent with regard to the cyclisation of the nitrophenyloxirane derivative (149b) to the 2,1-benzisoxazolone derivative (169b). However similar to the *trans* methylnitrophenyloxirane derivative (149a), the *trans* chloronitrophenyloxirane derivative (149b) was transformed into the corresponding 2,1-benzisoxazolone derivative (169b) in toluene in good yield (63%) using stannic chloride as the catalyst. The 2,1-benzisoxazolone derivative (169b) analysed correctly and had spectroscopic properties in good agreement with its structure. Confirmatory proof of

the 2,1-benzisoxazolone structure (169b) was provided by its conversion into the oxazine derivative (171b). Heating the 2,1-benzisoxazolone derivative (169b) under reflux in acetic anhydride gave the benzoxazine derivative (171b) in high yield (61%) whose combustion analysis and mass, IR and ^1H NMR spectra were in accord with its structure. In comparison with the reaction of the nitrophenyloxirane derivative (149b) with stannic chloride, heating the nitrophenyloxirane derivative (149b) with boron trifluoride etherate under reflux in dimethoxyethane gave the 2,1-benzisoxazolone derivative (169b) and the 2-aminobenzoic acid derivative (170b) each in low yields. The 2-aminobenzoic acid derivative (170b) analysed correctly and had spectroscopic data in accord with its structure. Further evidence for the 2-aminobenzoic acid derivative (170b) was obtained from its conversion into the corresponding benzoxazine derivative (171b), by heating under reflux in acetic anhydride.

Extension of the Lewis acid catalysed cyclisation of the nitrophenyloxirane derivatives (149a and b) to the 2,1-benzisoxazolone derivatives (169a and b) was carried out with the study of the effects of a strongly electron withdrawing group (nitro group) para to the side-chain in the nitrophenyloxirane derivative (169c). It was hoped that the dinitrophenyloxirane derivative (169c) would show interesting effects that contrast the results obtained from the reactions involving the methyl and chloronitrophenyloxirane derivatives (149a and b) with a Lewis acid. It was found that the *trans* dinitrophenyloxirane derivative (149c) also underwent similar Lewis acid-catalysed cyclisation reactions to that of the 4-methyl and 4-chloro derivatives (149a and b). Treating the *trans* nitrophenyloxirane derivative (149c) with stannic chloride in dichloromethane afforded a product in moderate yield (60%) which was assigned on the basis of IR and ^1H NMR spectra as the 2,1-benzisoxazolone derivative (169c). The mass spectrum of the 2,1-benzisoxazolone derivative (169c) showed no parent ion at m/z 314 for the 2,1-benzisoxazolone derivative (169c), but breakdown peaks at m/z 180 and 134 were present which are attributable to the splitting of the 2,1-benzisoxazolone derivative (169c) in the mass spectrum machine. Similar to the reaction of the nitrophenyloxirane derivative (149c) with stannic chloride, heating the nitrophenyloxirane derivative (149c) with boron trifluoride etherate under reflux in dimethoxyethane also afforded the 2,1-benzisoxazolone

derivative (169c) in moderate yield (53%). Unfortunately further studies on the Lewis acid catalysed cyclisation reaction of the nitrophenyloxirane derivative (149c) to the 2,1-benzisoxazolone derivative (169c) were terminated at this point due to time constraints.

5. CONCLUSIONS AND FUTURE WORK

It was found that (Schemes 26, 27 and 28) each of the 2-nitrobenzaldehyde derivatives (135a-c) were inefficient in reacting with a diacylmethane derivative (136) in the presence of hydrogen chloride to give the corresponding N-hydroxyquinolinone derivatives (138), (145) or (147). Preforming the benzylidene derivatives (137), (144) or (146) [which were originally proposed as intermediates in the hydrogen chloride catalysed reaction of the 2-nitrobenzaldehyde (135) with the diacylmethane derivative (136)] and reacting these derivatives with hydrogen chloride gave surprisingly only small quantities of the corresponding N-hydroxyquinolinone derivatives (138), (145) or (147). The mechanism of the hydrogen chloride catalysed reaction of the 2-nitrobenzaldehyde (135) with the diacylmethane derivative (136) to give a N-hydroxyquinolinone derivative (138), (145) or (147) is more complex than previously thought and is still not fully understood. Future work will involve studying the mechanism of this acid- catalysed reaction in greater detail. The substituent (electron donating or electron withdrawing) para to the side- chain in the benzylidene derivatives (137), (144) or (146) had no significant effect in promoting or inhibiting the cyclisation of the benzylidene derivatives (137), (144) or (146) to the N-hydroxyquinolinone derivatives (138), (145) or (147) in the presence of hydrogen chloride. Future work may involve looking at strongly electron withdrawing (trifluoromethyl group) and strongly electron donating (methoxy group) substituents para to the side- chain in nitrobenzylidene derivatives with regard to their effects on the acid- catalysed cyclisation of such derivatives to the corresponding N-hydroxyquinolinone derivatives.

As described in earlier work^{68,69} and also shown in these studies (Scheme 30) was that the *trans* nitrophenyloxirane derivatives (149a-c) reacted with hydrogen chloride

to give the dihydroxyquinolinone derivatives (152a-c) in poor yield. The substituent (electron withdrawing / donating) para to the side- chain in the nitrophenyloxirane derivatives (149a-c) exhibited no great influence with regard to promoting or inhibiting the acid- catalysed cyclisation of the nitrophenyloxirane derivatives (149a-c) to the dihydroxyquinolinone derivatives (152a-c). However the presence (Scheme 34) of a *cis* acyl group within the nitrophenyloxirane derivatives (150a-c) was particularly important in the hydrogen chloride catalysed cyclisation of the nitrophenyloxirane derivatives (150a-c) to the dihydroxyquinolinone derivatives (152a-c). The *cis* nitrophenyloxirane derivatives (150a-c) reacted with hydrogen chloride to afford the dihydroxyquinolinone derivatives (152a-c) in high yield. Future work will therefore entail studying other ways of obtaining *cis* nitrophenyloxirane derivatives which would be expected to cyclise to the corresponding dihydroxyquinolinone derivatives in the presence of hydrogen chloride.

The Lewis acid catalysed reactions (Scheme 37) of the nitrophenyloxirane derivatives (149a-c) gave as expected the 2,1-benzisoxazolone and 2-aminobenzoic acid derivatives (169a-c) and (170a-c). The substituent (Me, Cl, or NO₂) para to the side- chain in the nitrophenyloxirane derivatives showed no noticeable effect on the Lewis acid promoted cyclisation of the nitrophenyloxirane derivatives (149a-c) to the 2,1-benzisoxazolone derivatives (169a-c). Future work will involve investigating other substituents para to the side- chain in nitrophenyloxirane derivatives, such as methoxy (strongly electron donating) or trifluoromethyl (strongly electron withdrawing) groups with regard to whether the group para to the side- chain can influence the efficiency of the Lewis acid catalysed cyclisation of nitrophenyloxirane derivatives to 2,1-benzisoxazolone derivatives.

6. EXPERIMENTAL

General Experimental Details

Infrared spectra were recorded for Nujol suspensions or thin films using a Perkin-Elmer Paragon 1000 FT-IR spectrophotometer or BIO-RAD FTS-7 spectrophotometer. IR bands were strong and sharp unless specified as br (broad).

^1H NMR spectra were measured in the stated solvent at 200MHz using Bruker AC 250 and 200 spectrometers. Signals were sharp unless specified as; br = broad, d = doublet, dd = double doublet, t = triplet, q = quartet, or m = multiplet. ^{13}C NMR spectra were measured in the stated solvent at 50MHz using a Bruker AC 200 instrument or at 62.5MHz using a Bruker AC 250 instrument and were fully decoupled. Signals were sharp and quat = quaternary carbon atom. Quaternary carbon atoms and methylene groups were identified by $3\pi/4$ DEPT (Distortionless Enhancement by Polarisation Transfer) pulse sequence spectra.

Electron impact (EI) mass spectra were obtained using Kratos MS-50TC and profile instruments. Fast Atom Bombardment (FAB) mass spectra were recorded on a Kratos MS-50TC instrument for matrices in thioglycerol or 3-nitrobenzyl alcohol. Atmospheric Pressure Chemical Ionisation (APCI) and Electrospray (ES) mass spectra were obtained using a Micromass Platform II instrument.

Microanalyses were determined on a Perkin Elmer 2400 CHN Elemental Analysis instrument. Melting points (mp) of all analytical samples were determined on a Kofler hot-stage and are uncorrected. Routine melting points (mp) were carried out using a Griffin apparatus and are uncorrected.

All organic solvents were dried over anhydrous magnesium sulfate prior to evaporation under reduced pressure. Solvents were technical grade unless otherwise specified and unless otherwise indicated light petroleum had bp 60-80°C. Anhydrous solvents were dried as follows; Dimethylformamide and dichloromethane were distilled and stored over anhydrous 4Å molecular sieves. 1,4-Dioxane and 1,2-

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dimethoxyethane were distilled from calcium hydride and stored over 4Å molecular sieves. Ether and toluene were dried with sodium wire. Ethanol was distilled from magnesium and iodine and stored over 4Å molecular sieves. Tetrahydrofuran was distilled from sodium and benzophenone and stored over 4Å molecular sieves.

Wet column flash- chromatography was carried out over silica (Merck grade 60, type 9385). Thin Layer Chromatography (TLC) was carried out using Polygram SIL G/UV₂₅₄ precoated plastic sheets.

For X-ray analyses compounds were crystallised from ethyl acetate-light petroleum to give diffraction quality crystals. X-ray diffraction data were collected on a Stoe Stadi-4 four circle diffractometer on single crystals grown from the stated crystallisation solvent.

1-N,N-Dimethylamino-2-(2-nitroaryl)ethenes (134)

A solution of the corresponding 2-nitrotoluene derivative (133) (0.4mol) in anhydrous dimethylformamide (400ml) was stirred and treated with a solution of N,N-dimethylformamide dimethylacetal (95.2g; 0.8mol) in anhydrous dimethylformamide (400ml) and the mixture was then stirred and heated under reflux with the exclusion of atmospheric moisture for 18h. The resulting dark red solution was then worked up as described for the individual reactions below.

- (i) The mixture from 1,4-dimethyl-2-nitrotoluene (133a) was rotary evaporated under high vacuum (oil pump) to give 1-N,N-dimethylamino-2-(4-methyl-2-nitro)ethene (134a) as a red oil, which crystallised to give a red solid (97%), mp 38-40°C (from light petroleum), ν_{\max} 1516 and 1376 (NO₂) cm⁻¹, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 7.59-7.54 (2H, m, ArH), 7.30 (1H, d, J 13.4, CH), 7.26-7.21 (1H, m, ArH), 5.58 (1H, d, J 13.5, CH), 2.85 (6H, s, 2 x CH₃), and 2.26 (3H, s, CH₃).

Found: C, 64.1; H, 7.0; N, 13.6%; $m/z(\text{FABMS})$, 207 [(M+H)⁺].

C₁₁H₁₄N₂O₂ requires: C, 64.1; H, 6.8; N, 13.6%; M, 206.

(ii) The mixture from 4-chloro-2-nitrotoluene (133b) was rotary evaporated under high vacuum (oil pump) to give 1-N,N-dimethylamino-2-(4-chloro-2-nitrophenyl)ethene (134b) as a red oil, which crystallised to give a red solid (100%), mp 49-51°C (from light petroleum), ν_{\max} 1541 and 1376 (NO_2) cm^{-1} , $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 7.82-7.66 (2H, m, ArH), 7.46 (1H, d, J 13.3, CH), 7.42-7.37 (1H, m, ArH), 5.59 (1H, d, J 13.4, CH), and 2.89 (6H, s, 2 x CH_3).

Found: C, 53.2; H, 5.1; N, 12.3%; m/z (FABMS), 229, 227 $[(\text{M}+\text{H})^+]$.

$\text{C}_{10}\text{H}_{11}\text{ClN}_2\text{O}_2$ requires: C, 52.9; H, 4.8; N, 12.3%; M, 226.5.

(iii) The mixture from 2,4-dinitrotoluene (133c) was rotary evaporated under high vacuum (oil pump) to give a gummy dark red solid which was triturated with ether to afford 1-N,N-dimethylamino-2-(2,4-dinitrophenyl)ethene (134c) as a dark red solid (80%) which formed dark red microcrystals, mp 138-140°C (from ethanol- light petroleum), ν_{\max} 1513 and 1385 (NO_2) cm^{-1} , $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.53 (1H, d, J 2.4, ArH), 8.00-7.91 (2H, m, ArH), 7.77 (1H, d, J 9.4, CH), 5.87 (1H, d, J 13.0, CH), and 3.03 (6H, s, 2 x CH_3).

Found: m/z (HREIMS), 237.0754 (M^+).

$\text{C}_{10}\text{H}_{11}\text{N}_3\text{O}_4$ requires: M, 237.0750.

2-Nitrobenzaldehyde Derivatives (135)

A suspension of the corresponding 1-N,N-dimethylamino-2-(2-nitroaryl)ethene (134) (0.1mol) in tetrahydrofuran (500ml) was stirred and treated at room temperature with a solution of sodium periodate (64.2g; 0.3mol) in water, added in one portion. The mixture was then stirred at room temperature for 1h.

The mixture was filtered and the colourless inorganic cake was washed several times with ethyl acetate. The aqueous filtrate was washed several times with ethyl acetate and the total ethyl acetate extracts were washed with 10% w/v aqueous sodium

hydrogen carbonate solution (3 x 200ml) and rotary evaporated to give the crude product which was purified as described for the individual reactions below.

- (i) 1-N,N-Dimethylamino-2-(4-methyl-2-nitrophenyl)ethene (134a) gave a red oil which was triturated with ether to afford 4-methyl-2-nitrobenzaldehyde (135a) as a red solid (97%), mp 50-53°C (lit.,⁷¹ 55-56°C), which was used without further purification.
- (ii) 1-N,N-Dimethylamino-2-(4-chloro-2-nitrophenyl)ethene (134b) gave a gummy red solid which was triturated with ether to afford 4-chloro-2-nitrobenzaldehyde (135b) as a red solid (93%), mp 64-66°C (lit.,⁷⁹ 67-68°C) which was used without further purification.
- (iii) 1-N,N-Dimethylamino-2-(2,4-dinitrophenyl)ethene (134c) gave a dark red oil which was flash- chromatographed over silica.
Elution with hexane-dichloromethane (1:1) gave 2,4-dinitrobenzaldehyde (135c) as a red solid (68%), mp 65-67°C, identified by comparison (mp and IR spectrum) with an authentic sample.

Reactions of 2-Nitrobenzaldehyde Derivatives (135) with 1,3-Diacylmethane Derivatives (136) in Glacial Acetic Acid in the Presence of Piperidine

- (a) A solution of the corresponding 2-nitrobenzaldehyde derivative (135) (0.01mol) and the 1,3-diacylmethane derivative (136) (0.012mol) in glacial acetic acid (0.8mol) was stirred and treated with piperidine (1.0ml), added in one portion, and the mixture was stirred at room temperature with the exclusion of atmospheric moisture for 2h.
The resulting oily red mixture was treated with water (10.0ml) and extracted several times with dichloromethane to give the crude product which was purified as described for the individual reactions below.

- (i) Reaction of 4-chloro-2-nitrobenzaldehyde (135b) with pentane-2,4-dione (136a) gave a red oil which was triturated with ether to afford 3-acetyl-4-(2-

nitro-4-chlorophenyl)but-3-en-2-one (144a) as a brown solid (37%) which formed colourless microcrystals, mp 69-71°C (from ethanol- light petroleum), ν_{\max} 1703 (C=O), and 1523 and 1376 (NO₂) cm⁻¹, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.31 (1H, d, J 2.2, ArH), 8.03 (1H, s, CH), 7.92-7.87 (1H, m, ArH), 7.40 (1H, d, J 9.0, ArH), 2.44 (3H, s, CH₃), and 2.15 (3H, s, CH₃).

Found: C, 53.9; H, 3.8; N, 5.2%; m/z(FABMS), 270, 268 [(M+H)⁺].

C₁₂H₁₀ClNO₄ requires: C, 53.8; H, 3.7; N, 5.2%; M, 267.5.

- (ii) Reaction of 2,4-dinitrobenzaldehyde (135c) with pentane-2,4-dione (136a) gave a dark red oil which was flash- chromatographed over silica.

Elution with hexane-dichloromethane (3:7) gave 3-acetyl-4-(2,4-dinitrophenyl)but-3-en-2-one (146a) as a dark red oil (11%), ν_{\max} 1699 and 1674 (C=O), and 1532 and 1347(NO₂) cm⁻¹, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.86 (1H, d, J 2.3, ArH), 8.58 (1H, dd, J 8.4 and 2.4, ArH), 8.15 (1H, s, CH), 7.67 (1H, dd, J 8.5 and 0.4, ArH), 2.48 (3H, s, CH₃), and 2.19 (3H, s, CH₃).

Found: C, 51.7; H, 3.6; N, 10.1%; m/z(FABMS), 279 [(M+H)⁺].

C₁₂H₁₀N₂O₆ requires: C, 51.8; H, 3.6; N, 10.1%; M, 278.

- (iii) Repetition of the reaction conditions described in (a) before but with initial cooling at 0°C (ice- salt bath) gave a red oil which was flash- chromatographed over silica.

Elution with hexane-dichloromethane (2:3) gave a red oil (0.6g) which was triturated with ether to afford unreacted 2,4-dinitrobenzaldehyde (135c) as a yellow solid (37%), mp 62-65°C, which was identified by comparison (mp and IR spectrum) with an authentic sample.

Elution with hexane-dichloromethane (1:9) gave 3-acetyl-4-(2,4-dinitrophenyl)but-3-en-2-one (146a) as a red oil (39%) which was identified by comparison (IR spectrum) with a sample obtained before.

- (iv) Reaction of 4-methyl-2-nitrobenzaldehyde (135a) with 1-phenylbutane-1,3-dione (136b) gave a red oil which was flash- chromatographed over silica.

Elution with hexane-dichloromethane (3:2) gave unreacted 4-methyl-2-nitrobenzaldehyde (135a) as a red solid (24%), mp 52-54°C, which was identified by comparison (mp and IR spectrum) with a sample obtained before.

Elution with hexane-dichloromethane (1:1) gave 3-benzoyl-4-(4-methyl-2-nitrophenyl)but-3-en-2-one (137b) as a colourless solid (38%) which formed colourless microcrystals, mp 96-98°C (from ethanol), ν_{\max} 1681 and 1659 (C=O), and 1596 and 1347 (NO₂) cm⁻¹, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.34 (1H, s, CH), 7.96 (1H, d, J 0.8, ArH), 7.77-7.73 (2H, m, ArH), 7.57-7.53 (1H, m, ArH), 7.46-7.38 (3H, m, ArH), 7.15 (1H, d, J 7.9, ArH), 2.51 (3H, s, CH₃), and 2.31 (3H, s, CH₃).

Found: C, 69.8; H, 4.7; N, 4.6%; m/z(FABMS), 310 [(M+H)⁺].

C₁₈H₁₅NO₄ requires: C, 69.9; H, 4.9; N, 4.5%; M, 309.

- (v) Reaction of 4-chloro-2-nitrobenzaldehyde (135b) with 1-phenylbutane-1,3-dione (136b) gave a red oil which was flash- chromatographed over silica.

Elution with hexane-dichloromethane (1:4) gave 3-benzoyl-4-(4-chloro-2-nitrophenyl)but-3-en-2-one (144b) as a colourless solid (19%) which formed colourless microcrystals, mp 83-85°C (from ethanol), ν_{\max} 1671 (C=O), and 1596 and 1350 (NO₂) cm⁻¹, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.33 (1H, s, CH), 8.20 (1H, d, J 2.1, ArH), 7.79-7.73 (3H, m, ArH), 7.62-7.56 (1H, m, ArH), 7.47-7.41 (2H, m, ArH), 7.28 (1H, d, J 8.4, ArH), and 2.52 (3H, s, CH₃), $\delta_{\text{C}}[(\text{CD}_3)_2\text{SO}]$ 197.1 (quat.), 195.4 (quat.), 147.7 (quat.), 139.2 (CH), 135.9 (quat.), 134.8 (quat.), 134.3 (CH), 134.1 (CH), 131.9 (CH), 129.0 (2 x CH), 128.6 (2 x CH), 128.5 (quat.), 125.0 (CH), and 26.7 (CH₃).

Found: C, 61.8; H, 3.6; N, 4.2%; m/z(APCIMS), 332, 330 [(M+H)⁺].
C₁₇H₁₂ClNO₄ requires: C, 61.9; H, 3.6; N, 4.2%; M, 329.5.

- (vi) Reaction of 4-methyl-2-nitrobenzaldehyde (135a) with 1,3-diphenylpropane-1,3-dione (136c) gave a gummy red solid which was flash- chromatographed over silica.

Elution with hexane-dichloromethane (1:1) gave a gummy orange solid which was triturated with ether to afford 2-benzoyl-3-(4-methyl-2-nitrophenyl)-1-phenylprop-2-en-1-one (137c) as a yellow solid (6%) which formed pale yellow microcrystals, mp 122-124°C (from ethanol), ν_{\max} 1663(C=O), 1523 and 1373(NO₂) cm⁻¹, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.20-8.10 (4H, m, ArH), 7.92-7.91 (4H, m, ArH plus CH), 7.69-7.58 (6H, m, ArH), and 2.44 (3H, s, CH₃).

Found: C, 74.3; H, 4.6; N, 3.7%; m/z(HREIMS), 371.1147 (M⁺).
C₂₃H₁₇NO₄ requires: C, 74.4; H, 4.6; N, 3.8%; M, 371.1158.

- (vii) Reaction of 4-chloro-2-nitrobenzaldehyde (135b) with 1,3-diphenylpropane-1,3-dione (136c) gave a red oil which was flash- chromatographed over silica. Elution with hexane-dichloromethane (3:7) gave a red oil which was triturated with ether to afford 2-benzoyl-3-(4-chloro-2-nitrophenyl)-1-phenylprop-2-en-1-one (144c) as a colourless solid (8%) which formed colourless microcrystals, mp 120-122°C (from ethanol), ν_{\max} 1664 and 1651 (C=O), and 1532 and 1350 (NO₂) cm⁻¹, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.21 (1H, d, J 2.1, ArH), 8.01-7.97 (3H, m, ArH), 7.85-7.70 (4H, m, ArH plus CH), 7.69-7.58 (3H, m, ArH), and 7.57-7.41 (3H, m, ArH).

Found: C, 67.3; H, 3.8; N, 3.6%; m/z(APCIMS), 394, 392 [(M+H)⁺].
C₂₂H₁₄ClNO₄ requires: C, 67.4; H, 3.6; N, 3.6%; M, 391.5.

- (b) The reaction conditions described in (a) before were modified by stirring the reaction mixture at room temperature with the exclusion of atmospheric moisture

for 48h, then worked up as before and the crude product purified as described in the individual reactions below.

- (i) Reaction of 4-methyl-2-nitrobenzaldehyde (135a) with 1,3-diphenylpropane-1,3-dione (136c) gave a red oil which was flash- chromatographed over silica. Elution with hexane-dichloromethane (3:7) gave 2-benzoyl-3-(4-methyl-2-nitrophenyl)-1-phenylprop-2-en-1-one (137c) as a light brown solid (30%), mp 118-120°C, identified by comparison (mp and IR spectrum) with an authentic sample prepared before.
- (ii) Reaction of 4-chloro-2-nitrobenzaldehyde (135b) with 1,3-diphenylpropane-1,3-dione (136c) gave a red oil which was treated with ethanol and the resulting suspension filtered to afford 2-benzoyl-3-(4-chloro-2-nitrophenyl)-1-phenylprop-2-en-1-one (144c) as a brown solid (67%), mp 119-121°C, identified by comparison (mp and IR spectrum) with an authentic sample prepared before.
- (c) The reaction conditions described in (a) before were modified by stirring the reaction mixture at room temperature with the exclusion of atmospheric moisture for 66h, then worked up as before and the crude product purified as described in the individual reactions below.
 - (i) Reaction of 4-chloro-2-nitrobenzaldehyde (135b) with 1,3-diphenylpropane-1,3-dione (136c) gave a red oil which was triturated with ethanol to afford a brown solid which was combined with a second crop obtained by rotary evaporation of the ethanol mother liquor and flash- chromatography of the resulting red oil over silica eluting with hexane-dichloromethane (3:7) to give 2-benzoyl-3-(4-chloro-2-nitrophenyl)-1-phenylprop-2-en-1-one (144c) as an orange solid (96%), mp 118-120°C, identified by comparison (mp and IR spectrum) with an authentic sample prepared before.
- (d) The reaction conditions described in (a) before were modified by stirring the reaction mixture at room temperature with the exclusion of atmospheric moisture

for 72h, then worked up as before and the crude product purified as described in the individual reactions below.

- (i) Reaction of 4-methyl-2-nitrobenzaldehyde (135a) with 1-phenylbutane-1,3-dione (136b) gave a red oil which was flash- chromatographed over silica. Elution with hexane-dichloromethane (3:2) gave 3-benzoyl-4-(4-methyl-2-nitrophenyl)but-3-en-2-one (137b) as an orange solid (78%), mp 96-98°C, identified by comparison (mp and IR spectrum) with an authentic sample prepared before.
- (ii) Reaction of 4-chloro-2-nitrobenzaldehyde (135b) with 1-phenylbutane-1,3-dione (136b) gave a red oil which was flash- chromatographed over silica. Elution with hexane-dichloromethane (2:3) gave 3-benzoyl-4-(4-chloro-2-nitrophenyl)but-3-en-2-one (144b) as an orange solid (70%), mp 79-82°C, identified by comparison (mp and IR spectrum) with an authentic sample prepared before.
- (iii) Reaction of 4-methyl-2-nitrobenzaldehyde (135a) with ethyl 3-oxobutanoate (136d) gave a red oil which was flash- chromatographed over silica. Elution with hexane-dichloromethane (1:9) gave 3-ethoxycarbonyl-4-(4-methyl-2-nitrophenyl)but-3-en-2-one (137d) as an oily yellow mixture of *E* and *Z* isomers (25%), bp 180°C/0.1mmHg, ν_{\max} 1732, 1716 and 1694 (C=O), and 1531 and 1348 (NO₂) cm⁻¹, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.15 (1H, s, CH), 8.07 (1H, d, J 0.8, ArH), 8.05 (1H, d, J 0.9, ArH), 7.98 (1H, d, J 0.4, CH), 7.67-7.57 (2H, m, ArH), 7.33 (1H, d, J 8.0, ArH), 7.26 (1H, d, J 8.0, ArH), 4.28 (2H, q, J 7.1, CH₂), 4.04 (2H, q, J 7.1, CH₂), 2.42 (12H, s, 4 x CH₃), 1.27 (3H, t, J 7.1, CH₃), and 0.98 (3H, t, J 7.1, CH₃).

Found: C, 60.8; H, 5.5; N, 5.1%; $m/z(\text{FABMS})$, 278 [(M+H)⁺].

C₁₄H₁₅NO₅ requires: C, 60.6; H, 5.4; N, 5.1%; M, 277.

Reactions of 2-Nitrobenzaldehyde Derivatives (135) with 1,3-Diacylmethane Derivatives (136) in 1,2-Dimethoxyethane in the Presence of Piperidine

(a) A solution of the corresponding 2-nitrobenzaldehyde derivative (135) (0.01mol) and the 1,3-diacylmethane derivative (136) (0.012mol) in anhydrous 1,2-dimethoxyethane (25.0ml) was stirred and treated at room temperature with piperidine (0.1g). The mixture was then stirred at room temperature with the exclusion of atmospheric moisture for 2h.

The resulting orange- red solution was rotary evaporated and the crude product obtained was purified as described for the individual reactions below.

(i) Reaction of 2,4-dinitrobenzaldehyde (135c) with pentane-2,4-dione (136a) gave a red oil which was flash- chromatographed over silica.

Elution with hexane-dichloromethane (2:3) gave unreacted 2,4-dinitrobenzaldehyde (135c) as a red solid (46%), mp 66-68°C, identified by comparison (mp and IR spectrum) with an authentic sample prepared before.

Elution with hexane-dichloromethane (2:3) gave 3-acetyl-4-(2,4-dinitrophenyl)but-3-en-2-one (146a) as a red oil (54%), identified by comparison (IR spectrum) with an authentic sample prepared before.

(ii) Reaction of 2,4-dinitrobenzaldehyde (135c) with 1-phenylbutane-1,3-dione (136b) gave a red oil which was flash- chromatographed over silica.

Elution with hexane-dichloromethane (7:3) gave unreacted 2,4-dinitrobenzaldehyde (135c) as an orange- brown solid (51%), 64-66°C, identified by comparison (mp and IR spectrum) with an authentic sample prepared before.

Elution with hexane-dichloromethane (7:3) gave 3-benzoyl-4-(2,4-dinitrophenyl)but-3-en-2-one (146b) as an amber oil (47%), ν_{\max} 1733 and 1668 (C=O), and 1533 and 1346 (NO₂) cm⁻¹, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.76 (1H, d, J 2.3, ArH), 8.51-8.46 (1H, m, ArH), 8.44 (1H, s, ArH), 7.79-7.75 (2H, m, ArH), 7.64-7.41 (4H, m, ArH plus CH), and 2.56 (3H, s, CH₃).

Found: m/z (FABMS), 341.0774 [(M+H)⁺].

C₁₇H₁₂N₂O₆ requires: (M+H), 341.0774.

(b) The reaction conditions described in (a) before were modified by stirring the reaction mixture at room temperature with the exclusion of atmospheric moisture for 4h, then worked up as before and the product isolated and purified as described in the individual reactions below.

(i) Reaction of 4-chloro-2-nitrobenzaldehyde (135b) with pentane-2,4-dione (136a) gave a red oil which was flash- chromatographed over silica.

Elution with hexane-dichloromethane (3:2) gave unreacted 4-chloro-2-nitrobenzaldehyde (135b) as a red solid (30%), mp 64-66°C, identified by comparison (mp and IR spectrum) with an authentic sample prepared before.

Elution with hexane-dichloromethane (1:1) gave a brown oil which was triturated with light petroleum- ether to afford 3-acetyl-4-(4-chloro-2-nitrophenyl)but-3-en-2-one (144a) as a brown solid (38%), mp 66-68°C, identified by comparison (mp and IR spectrum) with an authentic sample obtained before.

(ii) Reaction of 4-chloro-2-nitrobenzaldehyde (135b) with 1-phenylbutane-1,3-dione (136b) gave a red oil which was flash- chromatographed over silica.

Elution with hexane-dichloromethane (3:7) gave a red oil which was triturated with ether- light petroleum to afford 3-benzoyl-4-(4-chloro-2-nitrophenyl)but-3-en-2-one (144b) as a brown solid (24%), mp 81-83°C, identified by comparison (mp and IR spectrum) with an authentic sample prepared before.

(iii) Reaction of 2,4-dinitrobenzaldehyde (135c) with 1-phenylbutane-1,3-dione (136b) gave a red oil which was flash- chromatographed over silica.

Elution with hexane-dichloromethane (7:3) gave a gummy red- brown solid which was triturated with ether to afford unreacted 2,4-dinitrobenzaldehyde

(135c) as a yellow solid (10%), mp 62-64°C, identified by comparison (mp and IR spectrum) with an authentic sample prepared before.

Further elution with hexane-dichloromethane (7:3) gave 3-benzoyl-4-(2,4-nitrophenyl)but-3-en-2-one (146b) as a red oil (77%), identified by comparison (IR spectrum) with an authentic sample obtained before.

(c) The reaction conditions described in (a) before were modified by stirring the reaction mixture at room temperature with the exclusion of atmospheric moisture for 24h, then worked up as before and the product was isolated and purified as described for the individual reactions below.

(i) Reaction of 4-methyl-2-nitrobenzaldehyde (135a) with 1-phenylbutane-1,3-dione (136b) gave a red oil which was flash- chromatographed over silica.

Elution with hexane-dichloromethane (3:7) gave 3-benzoyl-4-(4-methyl-2-nitrophenyl)but-3-en-2-one (137b) as a light brown solid (48%), mp 94-96°C, identified by comparison (mp and IR spectrum) with an authentic sample.

(d) The reaction conditions described in (a) before were modified by stirring the reaction mixture at room temperature with the exclusion of atmospheric moisture for 48h, then worked up as before and the product was isolated and purified as described for the individual reactions below.

(i) Reaction of 4-methyl-2-nitrobenzaldehyde (135a) with pentane-2,4-dione (136a) gave a red oil which was flash- chromatographed over silica.

Elution with hexane-dichloromethane (4:1) gave unreacted 4-methyl-2-nitrobenzaldehyde (135a) as a red solid (36%), mp 54-56°C, identified by comparison (mp and IR spectrum) with an authentic sample prepared before.

Elution with hexane-dichloromethane (7:3) gave 3-acetyl-4-(4-methyl-2-nitrophenyl)but-3-en-2-one (137a) as a colourless solid (43%), mp 107-109°C (from ethanol), ν_{\max} 1707 and 1666 (C=O), and 1524 and 1375 (NO₂) cm⁻¹, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.06 (2H, s, ArH plus CH), 7.63-7.58 (1H, m, ArH), 7.25 (1H, d, J 7.8, ArH), 2.43 (6H, s, 2 x CH₃), and 2.12 (3H, s, CH₃).

Found: C, 63.2; H, 5.3; N, 5.5%; m/z(EIMS), 247 (M^+).
 $C_{13}H_{13}NO_4$ requires: C, 63.2; H, 5.3; N, 5.7%; M, 247.

- (ii) Reaction of 4-chloro-2-nitrobenzaldehyde (135b) with pentane-2,4-dione (136a) gave a red oil which was flash- chromatographed over silica.

Elution with hexane-dichloromethane (3:2) gave 3-acetyl-4-(4-chloro-2-nitrophenyl)but-3-en-2-one (144a) as a pink solid (69%), mp 68-70°C, identified by comparison (mp and IR spectrum) with an authentic sample prepared before.

- (iii) Reaction of 4-methyl-2-nitrobenzaldehyde (135a) with 1-phenylbutane-1,3-dione (136b) gave a red oil which was flash- chromatographed over silica.

Elution with hexane-dichloromethane (7:3) gave 3-benzoyl-4-(4-methyl-2-nitrophenyl)but-3-en-2-one (137b) as a light red- brown solid (61%), mp 94-96°C, identified by comparison (mp an spectrum) with an authentic sample prepared before.

- (e) The reaction conditions described in (a) before were modified by stirring the reaction mixture at room temperature with the exclusion of atmospheric moisture for 72h, then worked up as before and the product was isolated and purified as described for the individual reactions below.

- (i) Reaction of 4-methyl-2-nitrobenzaldehyde (135a) with 1-phenylbutane-1,3-dione (136b) gave a red oil which was flash- chromatographed over silica.

Elution with hexane-dichloromethane (3:2) gave 3-benzoyl-4-(4-methyl-2-nitrophenyl)but-3-en-2-one (137b) as a light brown solid (40%), mp 95-97°C, identified by comparison (mp and IR spectrum) with an authentic sample prepared before.

The Attempted Reaction of 4-Methyl-2-nitrobenzaldehyde (135a) with 1,3-Diphenylpropane-1,3-dione (136c) in Ethanol in the Presence of Sodium Ethoxide

A solution of 4-methyl-2-nitrobenzaldehyde (135a) (0.83g; 0.005mol) in anhydrous ethanol (5.0ml) was stirred and treated at room temperature with a solution of 1,3-diphenylpropane-1,3-dione (136c) (1.1g; 0.005mol) in anhydrous ethanol (5.0ml) added in one portion. The resulting mixture was then cooled to 0°C (ice- salt bath) and treated dropwise with stirring at 0-5°C with a solution of sodium (0.12g; 0.005g.atom) in anhydrous ethanol (10.0ml). The mixture was then stirred in the melting ice-bath with the exclusion of atmospheric moisture for 18h.

The red solution was rotary evaporated and the residue was treated with water (10.0ml) then extracted several times with dichloromethane to give a red oil which was flash- chromatographed over silica.

Elution with hexane-dichloromethane (7:3) gave unreacted 1,3-diphenylpropane-1,3-dione (136c) as a light brown solid (0.25g), mp 75-77°C, identified by comparison (mp and IR spectrum) with an authentic sample.

Elution with hexane-dichloromethane (7:3) gave an orange solid (0.2g) whose TLC in hexane-dichloromethane (1:1) over silica showed it to be a mixture of the two starting materials which was not further investigated.

Elution with hexane-dichloromethane (7:3) gave unreacted 4-methyl-2-nitrobenzaldehyde (135a) (0.3g; 36%) as an orange solid, mp 53-55°C, identified by comparison (mp and IR spectrum) with an authentic sample.

Further elution with hexane-dichloromethane gave no other identifiable material.

3-Acetyl-6-chloro-1,4-dihydro-2,7-dimethyl-1-hydroxy-4-oxoquinoline (138a)

A solution of 4-methyl-2-nitrobenzaldehyde (135a) (0.83g; 0.005mol) in anhydrous ether (45.0ml) was stirred and treated with a solution of pentane-2,4-dione (136a) (0.5g; 0.005mol) in anhydrous ether (5.0ml) then the mixture was cooled to 0°C (ice-

salt bath) and treated with a slow stream of hydrogen chloride until saturated. The mixture was then securely stoppered and stored in a fridge for 19h.

The resulting red solution was rotary evaporated to give a gummy light brown solid (1.7g) which was triturated with ether to afford the N-hydroxy compound (138a) as an unstable colourless hydrochloride salt (1.0g; 66%), ν_{\max} 2428 br (OH), and 1699 (C=O) cm^{-1} , mp 278-280°C, crystallisation of which gave the parent N-hydroxy compound (138a) as colourless microcrystals, mp 278-280°C (from glacial acetic acid), ν_{\max} 3200-2000 br (OH), and 1685 (C=O) cm^{-1} , $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 12.09 (1H, s, OH), 8.07 (1H, s, ArH), 7.88 (1H, s, ArH), 2.49 (3H, s, CH₃), and 2.44 (6H, s, 2 x CH₃).

Found: C, 58.6; H, 4.7; N, 5.2%; m/z(FABMS), 268, 266 [(M+H)⁺].
C₁₃H₁₂ClNO₃ requires: C, 58.8; H, 4.5; N, 5.3%; M, 265.5.

Reactions of 4-Chloro-2-nitrobenzaldehyde (135b) with Pentane-2,4-dione (136a) in the Presence of Hydrogen Chloride

(a) A solution of 4-chloro-2-nitrobenzaldehyde (135b) (0.93g; 0.005mol) in anhydrous ether (45.0ml) was mixed with a solution of pentane-2,4-dione (136a) (0.5g; 0.005mol) in anhydrous ether (5.0ml) and the mixture was stirred, cooled to 0°C (ice- salt bath) and treated with a slow stream of hydrogen chloride until saturated. The mixture was securely stoppered and left in a fridge for 19h.

The resulting red solution was rotary evaporated to give an orange- brown gum which was treated with 10% w/v aqueous sodium hydrogen carbonate solution (5.0ml) and extracted several times with ether. Filtration of the resulting three phase mixture afforded 3-acetyl-6,7-dichloro-1,4-dihydro-1-hydroxy-4-oxoquinoline (145a) as a colourless solid (0.24g; 17%), which formed colourless microcrystals, mp 285-287°C (from glacial acetic acid-dimethylformamide), ν_{\max} 3095-2000 br (OH) and 1687 (C=O) cm^{-1} , $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.22 (1H, s, ArH), 8.08 (1H, s, ArH), 2.49 (3H, s, CH₃), and 2.44 (3H, s, CH₃).

Found: C, 50.0; H, 3.3; N, 4.9%; m/z(EIMS), 289, 287, 285 (M^+).
 $C_{12}H_9Cl_2NO_3$ requires: C, 50.3; H, 3.1; N, 4.9%; M, 286.

Rotary evaporation of the ethereal mother liquor gave 3-acetyl-4-(4-chloro-2-nitrophenyl)but-3-en-2-one (144a) as a light brown solid (0.66g; 49%), mp 69-71°C, identified by comparison (mp and IR spectrum) with an authentic sample prepared before.

- (b) Repetition of the reaction conditions described in (a) before but with resaturation of the reaction mixture with hydrogen chloride after 24h and then securely sealing the reaction mixture for a further 24h at 0°C, followed by the same work up gave the N-hydroxyquinoline derivative (145a) as a light brown solid (0.3g; 21%), mp 280-283°C, identified by comparison (mp and IR spectrum) with an authentic sample obtained in (a) before, and 3-acetyl-4-(4-chloro-2-nitrophenyl)but-3-en-2-one (144a) as a light brown solid (0.4g; 30%), mp 66-69°C, identified by comparison (mp and IR spectrum) with an authentic sample prepared before.
- (c) Repetition of the reaction conditions described in (a) before but for 48h at 0°C, followed by the same work up gave the N-hydroxyquinoline derivative (145a) as a light brown solid (0.15g; 11%), mp 276-280°C, identified by comparison (mp and IR spectrum) with an authentic sample obtained in (a) before, and 3-acetyl-4-(4-chloro-2-nitrophenyl)but-3-en-2-one (144a) as a light brown solid (0.6g; 45%), mp 66-69°C, identified by comparison (mp and IR spectrum) with an authentic sample prepared before.

Reaction of 2,4-Dinitrobenzaldehyde (135c) with Pentane-2,4-dione (136a) in the Presence of Hydrogen Chloride

A solution of 2,4-dinitrobenzaldehyde (135c)(0.78g; 0.004mol) in anhydrous 1,2-dimethoxyethane (30.0ml) was mixed with a solution of pentane-2,4-dione (136a) (0.4g; 0.004mol) in anhydrous 1,2-dimethoxyethane (10.0ml) and the mixture was stirred and cooled to 0°C (ice- salt bath) then treated with a slow stream of hydrogen

chloride until saturated. The resulting yellow solution was then securely stoppered and stored in a fridge for 24h.

The resulting yellow solution was rotary evaporated and the brown oil (1.2g) obtained was flash- chromatographed over silica.

Elution with hexane-dichloromethane (3:2) gave a mobile yellow oil (0.5g) which was triturated with ether- light petroleum to afford unreacted 2,4-dinitrobenzaldehyde (135c) as a pale yellow solid (0.22g; 28%), mp 65-67°C, identified by comparison (mp and IR spectrum) with an authentic sample obtained before.

Further elution with hexane-dichloromethane (1:1) gave 3-acetyl-4-(2,4-nitrophenyl)but-3-en-2-one (146a) as a red oil (0.7g; 63%), identified by comparison (IR spectrum and TLC in hexane-dichloromethane (1:2) over silica) with a sample obtained before.

Reaction of 4-Methyl-2-nitrobenzaldehyde (135a) with Ethyl 3-oxobutanoate (136d) in the Presence of Hydrogen Chloride

A solution of 4-methyl-2-nitrobenzaldehyde (135a) (0.83g; 0.005mol) in anhydrous ether (45.0ml) was mixed with a solution of ethyl 3-oxobutanoate (136d) (0.65g; 0.005mol) in anhydrous ether (5.0ml) and the solution was stirred and cooled to 0°C (ice- salt bath) then treated with a slow stream of hydrogen chloride until saturated. The mixture was then securely stoppered and stored in a fridge for 19h.

The resulting red solution was rotary evaporated to give a red- brown oil (1.8g) which was triturated with ether to afford the N-hydroxy compound (138d) as an unstable hydrochloride salt (0.5g; 30%), mp 195-197°C, ν_{\max} 3373(OH), and 1769(C=O) cm^{-1} , which on crystallisation gave the parent N-hydroxy compound (138d) as cream coloured microcrystals, mp 230-232°C (from ethanol), ν_{\max} 3500-2000 br (OH), and 1728(C=O) cm^{-1} , $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 12.11 (1H, br s, OH), 8.02 (1H, s, ArH), 7.87 (1H, s, ArH), 4.25 (2H, q, J 7.1, CH₂), 2.51 (3H, s, CH₃), 2.43 (3H, s, CH₃), and 1.28 (3H, t, J 7.1, CH₃).

Found: C, 56.6; H, 4.7; N, 4.7%.

C₁₄H₁₄ClNO₄ requires: C, 56.9; H, 4.7; N, 4.7%.

Found: m/z(HREIMS), 297.0585 (M⁺).

C₁₄H₁₄³⁷ClNO₄ requires: M, 297.0582.

Found: m/z(HREIMS), 295.0611 (M⁺).

C₁₄H₁₄³⁵ClNO₄ requires: M, 295.0611.

Work up of the ethereal mother liquor gave no other identifiable material.

The Reaction of 4-Methyl-2-nitrobenzaldehyde (135a) with Ethyl 3-Oxo-3-phenylpropanoate (136e) in the Presence of Hydrogen Chloride

A solution of 4-methyl-2-nitrobenzaldehyde (135a) (0.83g; 0.005mol) in anhydrous ether (45.0ml) was mixed with a solution of ethyl 3-Oxo-3-phenylpropanoate (136e) (0.96g; 0.005mol) in anhydrous ether (5.0ml) and the solution was stirred and cooled to 0°C (ice- salt bath) then treated with a slow stream of hydrogen chloride until saturated. The mixture was then securely stoppered and stored in a fridge for 19h.

The resulting red solution was rotary evaporated and the red oil (2.0g) obtained was treated with 10% aqueous sodium hydrogen carbonate solution (5.0ml) then extracted several times with ether to give a red oil (1.5g) which was flash-chromatographed over silica.

Elution with hexane-dichloromethane (1:1) gave unreacted 4-methyl-2-nitrobenzaldehyde (135a) (0.1g; 12%) as a red solid, mp 54-56°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

Further elution with hexane-dichloromethane (2:3) gave an orange oil (0.68g) which was triturated with ether to afford ethyl 2-benzoyl-3-(4-methyl-2-nitrophenyl)prop-2-enoate (137e) as a pale yellow solid (0.12g; 7%) which formed colourless microcrystals, mp 128-130°C (from ethanol), ν_{\max} 1718 and 1671 (C=O), and 1529 and 1377 (NO₂) cm⁻¹, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.28 (1H, d, J 0.3, ArH), 7.95 (1H, d, J 0.8, ArH), 7.80-7.76 (2H, m, ArH), 7.59-7.55 (1H, m, ArH), 7.49-7.40 (3H, m, ArH plus

CH), 7.15 (1H, d, J 7.9, ArH), 4.22 (2H, q, J 7.0, CH₂), 2.31 (3H, s, CH₃), and 1.14 (3H, t, J 7.1, CH₃).

Found: C, 67.6; H, 5.1; N, 4.0%; m/z(FABMS), 340 [(M+H)⁺].

C₁₉H₁₇NO₅ requires: C, 67.3; H, 5.0; N, 4.1%; M, 339.

The Attempted Reaction of 4-Methyl-2-nitrobenzaldehyde (135a) with 1-phenylbutane-1,3-dione (136b) in the Presence of Hydrogen Chloride

A solution of 4-methyl-2-nitrobenzaldehyde (135a) (0.83g; 0.005mol) in anhydrous ether (45.0ml) was mixed with a solution of 1-phenylbutane-1,3-dione (136b) (0.8g; 0.005mol) in anhydrous ether (5.0ml) and the solution was stirred and cooled to 0°C (ice- salt bath) then treated with a slow stream of hydrogen chloride until saturated. The mixture was then securely stoppered and stored in a fridge for 19h.

The resulting dark red solution was rotary evaporated and the red oil obtained was treated with 10% w/v aqueous sodium hydrogen carbonate solution (5.0ml) then extracted several times with ether to give a red oil (1.0g) which was flash-chromatographed over silica.

Elution with hexane-dichloromethane (3:2) gave unreacted 1-phenylbutane-1,3-dione (136b) (0.3g; 27%), mp 52-55°C, identified by comparison (mp and IR spectrum) with an authentic sample.

Further elution with hexane-dichloromethane (3:2) gave an orange oil (0.4g) whose TLC in hexane-dichloromethane (1:1) over silica showed it to be a mixture of the two starting materials which was not further investigated.

The Attempted Reaction of 4-Methyl-2-nitrobenzaldehyde (135a) with 1,3-Diphenylpropane-1,3-dione (136c) in the Presence of Hydrogen Chloride

A solution of 4-methyl-2-nitrobenzaldehyde (135a) (0.83g; 0.005mol) in anhydrous ether (45.0ml) was mixed with a solution of 1,3-diphenylpropane-1,3-dione (136c) (1.1g; 0.005mol) in anhydrous ether (5.0ml) and the solution was stirred and cooled

to 0°C (ice- salt bath) then treated with a slow stream of hydrogen chloride until saturated. The mixture was then securely stoppered and stored in a fridge for 19h.

The resulting red solution was rotary evaporated and the red oil obtained was treated with 10% w/v aqueous sodium hydrogen carbonate solution (5.0ml) then extracted several times with ether to give a red oil (1.6g) whose TLC in hexane-dichloromethane (1:1) showed it to be a mixture of the two starting materials which was not further investigated.

The Reaction of 3-Acetyl-4-(4-methyl-2-nitrophenyl)but-3-en-2-one (137a) with Hydrogen Chloride

A solution of 3-Acetyl-4-(4-methyl-2-nitrophenyl)but-3-en-2-one (137a) (1.2g; 0.005mol) in anhydrous ether (50.0ml) was stirred and cooled to 0°C (ice- salt bath) then treated with a slow stream of hydrogen chloride until saturated. The resulting yellow solution was then securely stoppered and stored in a fridge for 24h.

The yellow solution was rotary evaporated and the residual brown oil was triturated with ether to afford the colourless hydrochloride salt of 3-acetyl-6-chloro-1,4-dihydro-2,7-dimethyl-1-hydroxy-4-oxoquinoline (138a) (0.07g; 5%), mp 278-280°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

Rotary evaporation of the ethereal mother liquor gave unreacted alkene (137a) as a brown solid (1.1g; 92%), mp 104-106°C, which was identified by comparison (mp and IR spectrum) with a sample obtained before.

Attempted Cyclisation Reactions of the 4-(2-Nitrophenyl)but-3-en-2-one Derivatives (137), (144) and (146) in the Presence of Hydrogen Chloride

Solutions of the 4-(2-nitrophenyl)but-3-en-2-one derivatives (137), (144) and (146) (0.005mol) in anhydrous ether (50.0ml) were stirred and cooled to 0°C (ice- salt bath) then treated with a slow stream of hydrogen chloride until saturated. The resulting yellow- orange solutions were then securely stoppered and stored in a fridge for 24- 72h.

The yellow- orange mixtures were rotary evaporated and the residues were triturated with ether and the solids collected to afford the unreacted alkenone derivatives (137), (144) and (146) (80-100%), identified by comparison (mp and IR spectrum) with authentic samples prepared before.

1-Acetoxy-3-acetyl-6-chloro-1,4-dihydro-2,7-dimethyl-4-oxoquinoline (139)

3-Acetyl-6-chloro-1,4-dihydro-2,7-dimethyl-1-hydroxy-4-oxoquinoline (138a) (0.53g; 0.002mol) was treated with acetic anhydride (1.5ml) and the mixture was heated at 100°C (water bath) until it liquified. The resulting liquid mixture was then allowed to stand at room temperature for 20min.

The resulting gummy mixture was triturated with ether to afford the N-acetoxy compound (139) as a colourless solid (0.5g; 81%), which formed colourless microcrystals, mp 190°C(decomp.)(from ethyl acetate), ν_{\max} 1796 and 1684(C=O) cm^{-1} , $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.08 (1H, s, ArH), 7.63 (1H, s, ArH), 2.63 (3H, s, CH₃), 2.51 (3H, s, CH₃), 2.49 (3H, s, CH₃), and 2.30 (3H, s, CH₃).

Found: C, 58.3; H, 4.7; N, 4.5%; m/z (EIMS), 309, 307 (M^+).

$\text{C}_{15}\text{H}_{14}\text{ClNO}_4$ requires: C, 58.6; H, 4.6; N, 4.6%; M, 307.5.

Trans 2-Benzoyl-3-(2-nitrophenyl)oxirane Derivatives (149)

The corresponding 2-nitrobenzaldehyde derivative (135) (0.05mol) and 2-bromoacetophenone (148) (10.0g; 0.05mol) were suspended in methanol (150ml), and the suspension was stirred, cooled to 0-10°C (ice- bath) then treated dropwise with a solution of sodium (1.2g; 0.05g.atom) in methanol (50.0ml). The mixture was then stirred at room temperature with the exclusion of atmospheric moisture for 3h.

The resulting suspension was stirred and acidified to pH 6 by the dropwise addition of glacial acetic acid and the precipitated solid was collected, washed with a little ethanol and dried *in vacuo* to give the corresponding 2-benzoyl-3-(2-nitrophenyl)oxirane derivative (149) which was purified as described for the individual reactions below.

(i) 4-Methyl-2-nitrobenzaldehyde (135a) afforded *trans* 2-benzoyl-3-(4-methyl-2-nitrophenyl)oxirane (149a) as a colourless solid (72%), which formed colourless microcrystals, mp 116-118°C (from ethanol), ν_{\max} 1694 (C=O), and 1530 and 1377 (NO₂) cm⁻¹, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.11-8.04 (3H, m, ArH), 7.76-7.50 (5H, m, ArH), 4.73 (1H, d, J 2.1, CH), 4.53 (1H, d, J 2.1, CH), and 2.44 (3H, s, CH₃).

Found: C, 67.7; H, 4.6; N, 4.9%; m/z(FABMS), 284 [(M+H)⁺].

C₁₆H₁₃NO₄ requires: C, 67.8; H, 4.6; N, 4.9%; M, 283.

(ii) 4-Chloro-2-nitrobenzaldehyde (135b) afforded *trans* 2-benzoyl-3-(4-chloro-2-nitrophenyl)oxirane (149b) as a colourless solid (78%), which formed colourless microcrystals, mp 118-120°C (from ethanol), ν_{\max} 1698 (C=O), and 1529 and 1376 (NO₂) cm⁻¹, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.27 (1H, d, J 2.1, ArH), 8.12-8.07 (2H, m, ArH), 7.98-7.52 (5H, m, ArH), 4.78 (1H, d, J 2.1, CH), and 4.57 (1H, d, J 2.1, CH).

Found: C, 59.4; H, 3.4; N, 4.6%; m/z(EIMS), 303 (M⁺).

C₁₅H₁₀ClNO₄ requires: C, 59.2; H, 3.3; N, 4.6%; M, 303.5.

The Attempted Epimerisation of *Trans* 2-Benzoyl-3-(2-nitrophenyl)oxirane Derivatives (149)

A suspension of the corresponding *trans* 2-benzoyl-3-(2-nitrophenyl)oxirane derivative (149) (0.002mol) in methanol (50.0ml) was stirred and treated at room temperature with a solution of sodium methoxide in methanol [0.4ml of a 10% w/v solution of sodium (0.5g) in methanol (4.5ml)]. The solution was then stirred at room temperature with the exclusion of atmospheric moisture for 18h.

The resulting suspension was stirred and acidified by the dropwise addition of glacial acetic acid and the solid was collected, washed with a little ethanol and dried *in vacuo* to afford the unreacted oxirane derivatives (149) (80- 90%), identified by comparison (mp and IR spectra) with authentic samples prepared before.

The Attempted Reaction of 3-Acetyl-4-(4-chloro-2-nitrophenyl)but-3-en-2-one (144a) with Aqueous Sodium Hypochlorite in 1,4-Dioxane

A solution of the alkene derivative (144a) (0.54g; 0.002mol) in 1,4-dioxane (10.0ml) was stirred and treated with aqueous sodium hypochlorite solution (14-15% available chlorine; ca.2M)(5.0ml; 0.01mol), added in one portion. The mixture was then stirred at room temperature for 10min.

The solution was concentrated by rotary evaporation at as low a temperature as possible and the residue was treated with water (5.0ml) and then extracted several times with dichloromethane. The resulting three- phase mixture was filtered to remove a small quantity of solid and the dichloromethane layer was rotary evaporated to give a brown glass (0.2g), whose TLC in hexane-ethyl acetate (1:1) over silica showed it to be largely baseline material, which was not further investigated.

Rotary evaporation of the ethereal mother liquor gave only a dark red intractable oil (0.14g) which was not further investigated.

The Reaction of 3-Benzoyl-4-(2-nitrophenyl)but-3-en-2-one Derivatives (137b), (144b) and (146b) with Aqueous Sodium Hypochlorite in 1,4-Dioxane

A solution of the corresponding 3-benzoyl-4-(2-nitrophenyl)but-3-en-2-one derivative (137b), (144b) or (146b) (0.005mol) in 1,4-dioxane (25.0ml) was stirred and treated at room temperature with aqueous sodium hypochlorite solution (14-15% available chlorine; ca. 2M)(12.5ml; 0.025mol), added in one portion. The mixture was then stirred at room temperature for 10min.

The resulting yellow solution was concentrated by rotary evaporation at as low a temperature as possible and the residue was diluted with water (10.0ml) then extracted several times with dichloromethane to obtain the crude product which was purified as described for the individual reactions below.

- (a) 3-Benzoyl-4-(4-methyl-2-nitrophenyl)but-3-en-2-one (137b) afforded a yellow oil which was triturated with ether to afford *cis* 2-benzoyl-3-(4-methyl-2-nitrophenyl)oxirane (150a) as a pale yellow solid (55%) which formed colourless microcrystals, mp 129-131°C (from ethanol), ν_{\max} 1684 (C=O), and 1530 and 1380 (NO₂) cm⁻¹, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 7.92-7.85 (3H, m, ArH), 7.63-7.44 (5H, m, ArH), 5.20 (1H, d, J 5.1, CH), 5.03 (1H, d, J 5.1, CH), and 2.33 (3H, s, CH₃).

Found: C, 67.9; H, 4.5; N, 5.0%; m/z(FABMS), 284 [(M+H)⁺].

C₁₆H₁₃NO₄ requires: C, 67.8; H, 4.6; N, 4.9%; M, 283.

Rotary evaporation of the ethereal mother liquor gave a gummy orange solid which was flash- chromatographed in hexane-dichloromethane (1:4) over silica to afford *trans* 2-benzoyl-3-(4-methyl-2-nitrophenyl)oxirane (149a) as a light brown solid (12%), mp 110-113°C, identified by comparison (mp and IR spectrum) with a sample prepared before.

- (b) 3-Benzoyl-4-(4-chloro-2-nitrophenyl)but-3-en-2-one (144b) afforded a gummy light brown solid which was triturated with ether to afford *cis* 2-benzoyl-3-(4-chloro-2-nitrophenyl)oxirane (150b) as a colourless solid (52%) which formed colourless microcrystals, mp 153-155°C (from ethanol), ν_{\max} 1686 (C=O), and 1527 and 1344 (NO₂) cm⁻¹, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.09 (1H, d, J 2.1, ArH), 7.94-7.83 (3H, m, ArH), 7.67-7.45 (4H, m, ArH), 5.27 (1H, d, J 5.1, CH), and 5.05 (1H, d, J 5.1, CH).

Found: C, 59.1; H, 3.3; N, 4.6%; m/z(EIMS), 305, 303 (M⁺).

C₁₅H₁₀ClNO₄ requires: C, 59.2; H, 3.3; N, 4.6%; M, 303.5.

Rotary evaporation of the ethereal mother liquor gave a gummy orange solid which was flash- chromatographed in hexane-dichloromethane (3:7) over silica to afford *trans* 2-benzoyl-3-(4-chloro-2-nitrophenyl)oxirane (149b) as a yellow solid (12%), mp 111-114°C, identified by comparison (mp and IR spectrum) with a sample prepared before.

- (c) The amber coloured oil obtained from 3-benzoyl-4-(2,4-dinitrophenyl)but-3-en-2-one (146b) was flash- chromatographed over silica.

Elution with hexane-dichloromethane (3:2) gave *cis* 2-benzoyl-3-(2,4-dinitrophenyl)oxirane (150c) as a light brown solid (34%) which formed colourless microcrystals, mp 123-125°C (from ethanol), ν_{\max} 1693 (C=O), and 1532 and 1345 (NO₂) cm⁻¹, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.67 (1H, d, J 2.2, ArH), 8.61-8.56 (1H, m, ArH), 7.96-7.91 (3H, m, ArH), 7.69-7.60 (1H, m, ArH), 7.54-7.46 (2H, m, ArH), 5.37 (1H, d, J 5.2, CH), and 5.18 (1H, d, J 5.2, CH).

Found: C, 57.1; H, 3.1; N, 8.9%; m/z(EIMS), 314 (M⁺).

C₁₅H₁₀N₂O₆ requires: C, 57.3; H, 3.2; N, 8.9%; M, 314.

Elution with hexane-dichloromethane (3:2) gave *trans* 2-benzoyl-3-(2,4-dinitrophenyl)oxirane (149c) as a light brown solid (23%) which formed light brown microcrystals, mp 172-174°C (from ethanol- light petroleum), ν_{\max} 1688 (C=O), and 1527 and 1345 (NO₂) cm⁻¹, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.85 (1H, d, J 2.3, ArH), 8.67 (1H, dd, J 8.6 and 2.3, ArH), 8.12-8.08 (2H, m, ArH), 7.89 (1H, d, J 8.6, ArH), 7.77-7.76 (1H, m, ArH), 7.75-7.53 (2H, m, ArH), 4.87 (1H, d, J 2.2, CH), and 4.73 (1H, d, J 2.1, CH).

Found: C, 57.2; H, 3.1; N, 8.9%; m/z(EIMS), 314 (M⁺).

C₁₅H₁₀N₂O₆ requires: C, 57.3; H, 3.2; N, 8.9%; M, 314.

2,2-Dibenzoyl-3-(2-nitrophenyl)oxiranes (164)

- (a) A solution of the corresponding 2-benzoyl-3-(2-nitrophenyl)-1-phenylprop-2-en-1-one (137c) or (144c) (0.002mol) in 1,4-dioxane (10.0ml) was stirred and treated at room temperature with aqueous sodium hypochlorite solution (14-15% available chlorine; ca. 2M)(5.0ml; 0.01mol), added in one portion. The mixture was then stirred at room temperature for 10min.

The resulting solution was concentrated by rotary evaporation at as low a temperature as possible then diluted with water (5.0ml) and extracted several

times with dichloromethane to give the crude product as an orange oil. This was triturated with ether to afford the corresponding 2,2-dibenzoyl-3-(2-nitrophenyl)oxirane (164) which was purified as described for the individual reactions below.

- (i) 2-Benzoyl-3-(4-methyl-2-nitrophenyl)-1-phenylprop-2-en-1-one (137c) afforded 2,2-dibenzoyl-3-(4-methyl-2-nitrophenyl)oxirane (164a; $R^1=Ph$; $R^2=Ph$) as a colourless solid (66%) which formed colourless microcrystals, mp 140-142°C (from ethanol), ν_{max} 1677 (C=O), and 1528 and 1348 (NO₂) cm⁻¹, $\delta_H[(CD_3)_2SO]$ 8.08-8.01 (3H, m, ArH), 7.90-7.86 (2H, m, ArH), 7.71-7.35 (8H, m, ArH), 5.43 (1H, s, CH), and 2.35 (3H, s, CH₃).

Found: C, 71.3; H, 4.5; N, 3.5%; m/z (EIMS), 387 (M⁺).

C₂₃H₁₇NO₅ requires: C, 71.3; H, 4.4; N, 3.6%; M, 387.

- (ii) 2-Benzoyl-3-(4-chloro-2-nitrophenyl)-1-phenylprop-2-en-1-one (144c) afforded 2,2-dibenzoyl-3-(4-chloro-2-nitrophenyl)oxirane (164b; $R^1=Ph$; $R^2=Ph$) as a colourless solid (49%) which formed colourless microcrystals, mp 126-128°C (from ethanol), ν_{max} 1676 (C=O), and 1523 and 1344 (NO₂) cm⁻¹, $\delta_H[(CD_3)_2SO]$ 8.26 (1H, d, J 2.1, ArH), 8.08-8.03 (2H, m, ArH), 7.89-7.82 (3H, m, ArH), 7.68-7.42 (7H, m, ArH), and 5.45 (1H, s, CH₃).

Found: C, 64.5; H, 3.3; N, 3.4%; m/z (EIMS), 409, 407 (M⁺).

C₂₂H₁₄ClNO₅ requires: C, 64.8; H, 3.4; N, 3.4%; M, 407.5.

- (iii) Repetition of the reaction described in (ii) before but at room temperature for 30min followed by the same work up gave the oxirane derivative (164b; $R^1=Ph$; $R^2=Ph$) as a colourless solid (44%), mp 118-121°C, identified by comparison (mp and IR spectrum) with a sample prepared in (ii) before.
- (iv) Repetition of the reaction described in (ii) before but at 11°C (ice bath) for 5min followed by the same work up gave the oxirane derivative (164b;

$R^1=Ph$; $R^2=Ph$) as a colourless solid (27%), mp 123-125°C, identified by comparison (mp and IR spectrum) with a sample prepared in (ii) before.

- (b) A solution of 2-benzoyl-3-(4-chloro-2-nitrophenyl)-1-phenylprop-2-en-1-one (144c) (0.78g; 0.002mol) in Analar pyridine (5.0ml) was stirred at room temperature and treated with aqueous sodium hypochlorite solution (10-14% available chlorine; ca. 2M)(5.0ml; 0.01mol), added in one portion. The mixture was then stirred at room temperature for 10min.

The resulting solution was treated with 2M aqueous hydrochloric acid (40.0ml) and stirred at room temperature for 5min. The resulting gummy mixture was extracted several times with dichloromethane to give an orange oil which was triturated with ether to afford 2,2-dibenzoyl-3-(4-chloro-2-nitrophenyl)oxirane (164b; $R^1=Ph$; $R^2=Ph$) as a yellow solid (0.2g; 25%), mp 122-124°C, which was identified by comparison (mp and IR spectrum) with a sample obtained before.

6-Chloro-1,4-dihydro-1,3-dihydroxy-4-oxo-2-phenylquinolines (152)

- (a) A solution of the corresponding oxirane derivative (149) or (150) (0.01mol) in anhydrous 1,2-dimethoxyethane (100ml) was stirred and cooled to 0°C (ice- salt bath), then treated with a slow stream of hydrogen chloride until saturated. The resulting red brown solution was then securely stoppered and stored in a fridge for 24h.

The red- brown mixture was rotary evaporated and the crude product obtained was purified as described in the individual reactions below.

- (i) *Trans* 2-benzoyl-3-(4-methyl-2-nitrophenyl)oxirane (149a) gave a gummy brown solid which was triturated with ether to afford 6-chloro-1,4-dihydro-1,3-dihydroxy-7-methyl-4-oxo-2-phenylquinoline (152a) as a light brown solid (57%), which formed colourless microcrystals, mp 260-262°C (from ethanol), ν_{\max} 3345, 3090 br, and 2432 br (OH), and 1589 (C=O) cm^{-1} , $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 11.80 (1H, br s, OH)(exch.), 8.15 (1H, s, ArH), 7.79 (1H, s, ArH), 7.50 (1H, s, ArH), and 2.50 (3H, s, CH_3).

Found: C, 63.7; H, 4.0; N, 4.4%; m/z(FABMS), 304, 302 [(M+H)⁺].
C₁₆H₁₂ClNO₃ requires: C, 63.7; H, 4.0; N, 4.6%; M, 301.5.

Rotary evaporation of the ethereal mother liquor gave a red oil which was treated with 10% w/v aqueous sodium hydrogen carbonate solution (10.0ml). The mixture was extracted several times with dichloromethane and the combined dichloromethane extracts were rotary evaporated to give a red oil which was flash- chromatographed in hexane-dichloromethane (3:2) over silica to give 1-phenyl-3-(4-methyl-2-nitrophenyl)propane-1,2-dione (151a) as a yellow solid (16%) which formed yellow microcrystals, mp 78-80°C (from ethanol), ν_{\max} 1716 and 1667 (C=O), and 1531 and 1377 (NO₂) cm⁻¹, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 7.99-7.93 (3H, m, ArH), 7.80-7.74 (2H, m, ArH), 7.64-7.55 (3H, m, ArH), 4.68 (2H, s, CH₂), and 2.42 (3H, s, CH₃).

Found: C, 67.6; H, 4.5; N, 4.8%; m/z(EIMS), 283 (M⁺).
C₁₆H₁₃NO₄ requires: C, 67.8; H, 4.6; N, 4.9%; M, 283.

- (ii) *Cis* 2-benzoyl-3-(4-methyl-2-nitrophenyl)oxirane (150a) gave a gummy orange solid which was triturated with ether to afford the hydrochloride salt of 6-chloro-1,4-dihydro-1,3-dihydroxy-7-methyl-4-oxo-2-phenylquinoline (152a) as an orange solid (86%) which formed colourless microcrystals, mp 207-209°C (from ethanol), ν_{\max} 3500-2200 br (OH and NH⁺), and 1584 (C=O) cm⁻¹, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.21 (1H, s, ArH), 7.88 (1H, s, ArH), 7.55-7.50 (5H, m, ArH), and 2.49 (3H, s, CH₃).

Found: C, 56.5; H, 4.0; N, 4.1%; m/z(EIMS), 301 [(M-HCl)⁺].
C₁₆H₁₃Cl₂NO₃ requires: C, 56.8; H, 3.8; N, 4.1%; M, 338.

The hydrochloride salt of the N- hydroxy compound (152a) was treated with 10% w/v aqueous sodium hydrogen carbonate solution (12.5ml) then stirred at room temperature for 2h. The insoluble sodium salt was collected, suspended in 2M aqueous hydrochloric acid (12.5ml) and the suspension stirred at room

temperature for 2h and filtered to afford the free N- hydroxy compound (152a) as a light brown solid (86%), mp 256-259°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

- (iii) *Trans* 2-benzoyl-3-(4-chloro-2-nitrophenyl)oxirane (149b) gave a gummy orange solid which was triturated with ether to afford 6,7-dichloro-1,4-dihydro-1,3-dihydroxy-4-oxo-2-phenylquinoline (152b) as an orange- yellow solid (50%), which formed yellow microcrystals, mp 202-204°C (from ethanol), ν_{\max} 3409 br and 3200-2000 br (OH), and 1574 (C=O) cm^{-1} , $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.33 (1H, s, ArH), 8.05 (1H, s, ArH), 7.55-7.49 (5H, m, ArH), and 4.20 (2H, br s, OH)(exch.).

Found: C, 56.1; H, 2.9; N, 4.2%; m/z (APCIMS), 326, 324, 322 (M^+).
 $\text{C}_{15}\text{H}_9\text{Cl}_2\text{NO}_3$ requires: C, 56.1; H, 2.8; N, 4.4%; M, 321.

The ethereal mother liquor was rotary evaporated and the resulting red oil was treated with 10% w/v aqueous sodium hydrogen carbonate solution (10.0ml) then extracted several times with dichloromethane and the combined extracts rotary evaporated to give a red oil which was flash- chromatographed over silica.

Elution with hexane-dichloromethane (3:2) gave 1-phenyl-3-(4-chloro-2-nitrophenyl)propane-1,2-dione (151b) as a yellow solid (19%) which formed yellow microcrystals, mp 80-82°C (from ethanol), ν_{\max} 1715 and 1663 (C=O), and 1530 and 1348 (NO_2) cm^{-1} , $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.23 (1H, d, J 2.2, ArH), 8.00-7.88 (2H, m, ArH), 7.87-7.71 (2H, m, ArH), 7.68 (1H, s, ArH), 7.65-7.56 (2H, m, ArH), and 4.74 (2H, s, CH_2).

Found: C, 59.1; H, 3.2; N, 4.6%; m/z (EIMS), 305, 303 (M^+).
 $\text{C}_{15}\text{H}_{10}\text{ClNO}_4$ requires: C, 59.3; H, 3.3; N, 4.6%; M, 303.5.

Further elution with hexane-dichloromethane (1:1) gave 1-benzoyl-2-chloro-1-hydroxy-2-(4-chloro-2-nitrophenyl)ethane (153b) as a red solid (21%)

which formed colourless microcrystals, mp 112-114°C (from ethanol), ν_{\max} 3416 (OH), 1668 (C=O), and 1592 and 1338 (NO₂) cm⁻¹, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.14-7.55 (8H, m, ArH), 6.71 (1H, dd, J 3.7 and 1.5, OH)(exch.), and 5.72-5.70 (2H, m, CH).

Found: C, 52.8; H, 3.2; N, 4.0%; m/z(FABMS), 344, 342, 340 [(M+H)⁺].
C₁₅H₁₁Cl₂NO₄ requires: C, 52.9; H, 3.2; N, 4.1%; M, 340.

- (iv) *Cis* 2-benzoyl-3-(4-chloro-2-nitrophenyl)oxirane (150b) gave a gummy orange solid which was triturated with ether to afford the N- hydroxy compound (152b) as a light brown solid (93%), mp 190-193°C, identified by comparison (mp and IR spectrum) with an authentic sample prepared in (iii) before.
- (v) *Trans* 2-benzoyl-3-(2,4-dinitrophenyl)oxirane (149c) gave a viscous amber oil which was triturated with ether- ethyl acetate to afford the unreacted oxirane starting material (149c) as a yellow solid (54%), mp 168-170°C, which was identified by comparison (mp and IR spectrum) with a sample obtained before.
- (vi) *Cis* 2-benzoyl-3-(2,4-dinitrophenyl)oxirane (150c) gave a gummy orange solid which was triturated with ether to afford 6-chloro-1,4-dihydro-1,3-dihydroxy-7-nitro-4-oxo-2-phenylquinoline (152c) as an unstable orange-brown hydrochloride salt (73%), mp 307-310°C, ν_{\max} 3096 and 2761 (OH) cm⁻¹, which gave the free N- hydroxy compound (152c) on crystallisation as yellow microcrystals, mp 310-312°C (from ethanol), ν_{\max} 2629 br (OH), and 1577 (C=O) cm⁻¹, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 12.23 (1H, br s, OH)(exch.), 8.39 (1H, s, ArH), 8.29 (1H, s, ArH), 7.83-7.68 (2H, m, ArH), and 7.62-7.56 (3H, m, ArH).

Found: C, 54.6; H, 2.7; N, 8.5%.

C₁₅H₉ClN₂O₅ requires: C, 54.1; H, 2.7; N, 8.4%.

Found: m/z(HREIMS), 332.0009 (M⁺).

C₁₅H₉³⁷ClN₂O₅ requires: M, 332.0014.

Found: m/z(HREIMS), 330.0039 (M⁺).

C₁₅H₉³⁵ClN₂O₅ requires: M, 330.0044.

- (vii) Repetition of the reaction described in (vi) before but at 0°C for 72h followed by the same work up afforded the N- hydroxyquinoline derivative (152c) as a yellow solid (76%), mp 308-310°C, which was identified by comparison (mp and IR spectrum) with a sample obtained before.
- (b) The general reaction conditions described in (a) before were repeated but in anhydrous 1,4-dioxane at 11°C (ice- water bath) and the resulting red- brown solution securely stoppered, stored in a fridge for 24h then worked up as described for the individual reactions below.
- (i) The mixture from *trans* 2-benzoyl-3-(4-methyl-2-nitrophenyl)oxirane (149a), containing suspended solid, was rotary evaporated and the residue triturated with ether to afford the hydrochloride salt of 6-chloro-1,4-dihydro-1,3-dihydroxy-7-methyl-4-oxo-2-phenylquinoline (152a) as a colourless solid (45%) which formed colourless microcrystals, mp 207-209°C (from ethanol), identical (mp and IR spectrum) to a sample prepared before.
- (ii) The mixture from *trans* 2-benzoyl-3-(4-chloro-2-nitrophenyl)oxirane (149b), containing suspended solid, was rotary evaporated and the residue triturated with ether to afford the hydrochloride salt of 6,7-dichloro-1,4-dihydro-1,3-dihydroxy-4-oxo-2-phenylquinoline (152b) as a colourless solid (24%), mp 165-169°C, ν_{\max} 3141- 2695 br (OH and NH⁺) which gave the free N- hydroxy compound (152b) on crystallisation as yellow microcrystals, mp 202-204°C (from ethanol), identical (mp and IR spectrum) to a sample prepared before.

Rotary evaporation of the ethereal mother liquor gave a red oil which was treated with 10% w/v aqueous sodium hydrogen carbonate solution (12.5ml)

then extracted several times with dichloromethane. Rotary evaporation of the combined dichloromethane extracts gave a red oil which was flash-chromatographed over silica.

Elution with hexane-dichloromethane (1:1) gave 1-phenyl-3-(4-chloro-2-nitrophenyl)propane-1,2-dione (151b) as an orange- yellow solid (16%), mp 80-82°C, identical (mp and IR spectrum) to a sample prepared before.

Further elution with hexane-dichloromethane (3:7) gave 1-benzoyl-2-chloro-1-hydroxy-2-(4-chloro-2-nitrophenyl)ethane (153b) as a beige solid (15%), mp 112-114°C, identical (mp and IR spectrum) to a sample prepared before.

- (c) A solution of *trans* 2-benzoyl-3-(4-methyl-2-nitrophenyl)oxirane (149a) (0.56g; 0.002mol) in anhydrous dichloromethane (20.0ml) was stirred and cooled to 0°C (ice- salt bath) then treated with a slow stream of hydrogen chloride until saturated. The mixture was then securely stoppered and stored in a fridge for 24h.

The mixture, containing suspended solid, was filtered, and the solid gently warmed in ethanol (2.0ml) and hot filtered to obtain 6-chloro-3,4-dihydro-3,4-dioxo-7-methyl-2-phenylquinoline 1-N-oxide (157a) as a red solid (0.03g; 5%) which formed red microcrystals, mp 205-207°C (from glacial acetic acid), ν_{\max} 1704 and 1651 (C=O) cm^{-1} , $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.19 (2H, br s, ArH), 7.51 (5H, s, ArH), and 2.50 (3H, s, CH_3).

Found: $m/z(\text{HREIMS})$, 301.0316 (M^+).

$\text{C}_{16}\text{H}_{10}^{37}\text{ClNO}_3$ requires: M, 301.0320.

Found: $m/z(\text{HREIMS})$, 299.0350 (M^+).

$\text{C}_{16}\text{H}_{10}^{35}\text{ClNO}_3$ requires: M, 299.0349.

Rotary evaporation of the ethanolic mother liquor afforded the hydrochloride salt of the N- hydroxy compound (152a) (0.3g; 49%), mp 195-198°C, identified by comparison (mp and IR spectrum) with an authentic sample obtained before.

Work up of the dichloromethane mother liquor gave no further identifiable material.

(d) A solution of *trans* 2-benzoyl-3-(4-methyl-2-nitrophenyl)oxirane (149a) (1.1g; 0.004mol) in glacial acetic acid (20.0ml) was stirred and cooled to 17°C (ice-water bath) then treated with a slow stream of hydrogen chloride until saturated. The resulting orange mixture was then securely stoppered and stored in a fridge for 24h.

The resulting suspension was filtered and the solid washed with ether to afford the hydrochloride salt of the N- hydroxy compound (152a) (0.42g; 35%), mp 198-202°C, which was identified by comparison (mp and IR spectrum) with a sample obtained before.

Work up of the glacial acetic acid- ether mother liquor gave no other identifiable material.

6-Chloro-1,4-dihydro-3-hydroxy-4-oxo-2-phenylquinolines (158)

A solution of the corresponding 6-chloro-1,3-dihydroxy-4-oxo-quinoline derivative (152) (0.005mol) in 70% w/v aqueous ethanol (100ml) was treated with an equal weight of sodium dithionite, added in one portion and the mixture was stirred and heated under reflux for 0.5h. A second equal weight of sodium dithionite was then added and stirring and heating under reflux was continued for a further 0.5h.

The resulting suspension was rotary evaporated and the residue treated with water (10.0ml) and filtered to give the crude product which was purified as described for the individual reactions below.

(i) 6-Chloro-1,4-dihydro-1,3-dihydroxy-7-methyl-4-oxo-2-phenylquinoline (152a) afforded 6-chloro-1,4-dihydro-3-hydroxy-7-methyl-4-oxo-2-phenylquinoline (158a) as a colourless solid (93%), which formed colourless microcrystals, mp 292-294°C (from glacial acetic acid), ν_{\max} 3226 br and 3115 br (NH or OH), and 1628 (C=O) cm^{-1} , $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 11.60 (1H, br s, NH or OH), 8.07 (1H, s, ArH), 7.80-7.74 (2H, m, ArH), 7.65 (1H, s, ArH), and 7.61-7.54 (3H, m, ArH).

Found: C, 66.8; H, 4.2; N, 4.9%.

C₁₆H₁₂ClNO₂ requires: C, 67.3; H, 4.2; N, 4.9%.

Found: m/z(HREIMS), 287.0523 (M⁺).

C₁₆H₁₂³⁷ClNO₂ requires: M, 287.0527.

Found: m/z(HREIMS), 285.0563 (M⁺).

C₁₆H₁₂³⁵ClNO₂ requires: M, 285.0557.

(ii) 6,7-Dichloro-1,4-dihydro-1,3-dihydroxy-4-oxo-2-phenylquinoline (152b)

afforded 6,7-dichloro-1,4-dihydro-3-hydroxy-4-oxo-2-phenylquinoline (158b) as a yellow solid (87%), which formed yellow microcrystals, mp 300-302°C (from glacial acetic acid), ν_{\max} 3418 (OH or NH), 3122 br (OH or NH), and 1632 (C=O) cm⁻¹, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 11.96-11.82 (1H, br s, NH), 8.24 (1H, s, ArH), 8.02 (1H, s, ArH), 7.82 (1H, br s, OH), and 7.58-7.49 (5H, m, ArH).

Found: C, 58.6; H, 2.8; N, 4.5%; m/z(APCIMS), 309, 307, 305 (M⁺).

C₁₅H₉Cl₂NO₂ requires: C, 58.8; H, 2.9; N, 4.6%; M, 306.

(iii) 6-Chloro-1,4-dihydro-1,3-dihydroxy-7-nitro-4-oxo-2-phenylquinoline (152c)

afforded 7-amino-6-chloro-1,4-dihydro-3-hydroxy-4-oxo-2-phenylquinoline (168) as a yellow-brown solid (82%), which formed yellow-brown microcrystals, mp 285-287°C (from dimethylformamide-ethyl acetate), ν_{\max} 3700-2000 br (OH and NH⁺), and 1637 (C=O) cm⁻¹, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 12.97 (1H, s, NH or OH)(exch.), 8.40 (1H, s, ArH), 8.05-8.02 (2H, m, ArH), 7.86-7.81 (3H, m, ArH), and 7.35 (1H, s, ArH).

Found: m/z(HREIMS), 289.0557 (M⁺).

C₁₅H₁₁³⁷ClN₂O₂ requires: M, 289.0558.

Found: m/z(HREIMS), 287.0588 (M⁺).

C₁₅H₁₁³⁵ClN₂O₂ requires: M, 287.0587.

Attempted Catalytic Hydrogenation Reactions of 6-Chloro-1,4-dihydro-1,3-dihydroxy-7-nitro-4-oxo-2-phenylquinoline (152c)

- (a) A solution of the nitro N-hydroxyquinoline derivative (152c) (0.001mol) in ethanol (30.0ml) was hydrogenated over 10% palladium-on-charcoal (10% by weight) at room temperature and atmospheric pressure until no further hydrogen was absorbed.

The mixture was filtered through Celite and the filtrate was rotary evaporated to afford a dark red oil flash- chromatography of which over silica yielded no identifiable material.

- (b) Repetition of the reaction described in (a) before but in glacial acetic acid as solvent gave a viscous brown oil whose TLC in ethyl acetate over silica showed it to be a multicomponent mixture which yielded no identifiable material.

6-Chloro-3,4-dihydro-3,4-dioxo-2-phenylquinoline 1-N-oxides (157)

- (a) A solution of the corresponding 6-chloro-1,4-dihydro-1,3-dihydroxy-4-oxo-2-phenylquinoline derivative (152) (0.002mol) in anhydrous dimethylformamide (20.0ml) was stirred and treated at room temperature with activated manganese dioxide (Aldrich 21,764-6)(1.0g) added in one portion. The mixture was then stirred at room temperature with the exclusion of atmospheric moisture for 1h.

The resulting suspension was filtered through Celite and the filter pad washed several times with anhydrous dimethylformamide. Rotary evaporation of the combined filtrate and washings under high vacuum (oil pump) gave a gummy red solid. This was washed with anhydrous ether to give the crude 3,4-dioxoquinoline 1-N-oxide (157) which was purified as described for the individual reactions below.

- (i) 6-Chloro-1,4-dihydro-1,3-dihydroxy-7-methyl-4-oxo-2-phenylquinoline (152a) afforded 6-chloro-3,4-dihydro-3,4-dioxo-7-methyl-2-phenylquinoline 1-N-oxide (157a) as a red solid (93%), which formed red microcrystals, mp 205-

207°C (from glacial acetic acid), identical (mp and IR spectrum) to a sample prepared before.

- (ii) 6-Chloro-1,4-dihydro-1,3-dihydroxy-7-nitro-4-oxo-2-phenylquinoline (152c) afforded 6-chloro-3,4-dihydro-3,4-dioxo-7-nitro-2-phenylquinoline 1-N-oxide (157c) as a red solid (79%), which formed red microcrystals, mp 240-242°C (from glacial acetic acid), ν_{\max} 1718 and 1654 (C=O) cm^{-1} , $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.85 (1H, s, ArH), 8.41 (1H, br s, ArH), and 7.54 (5H, s, ArH).

Found: C, 54.3; H, 2.2; N, 8.4%; $m/z(\text{EIMS})$, 332, 330 (M^+).

$\text{C}_{15}\text{H}_7\text{ClN}_2\text{O}_5$ requires: C, 54.5; H, 2.1; N, 8.5%; M, 330.5.

- (b) A solution of 6,7-dichloro-1,4-dihydro-1,3-dihydroxy-4-oxo-2-phenylquinoline (152b) (0.64g;0.002mol) in anhydrous tetrahydrofuran (20.0ml) was stirred and treated at room temperature with activated manganese dioxide (Aldrich 21,764-6)(1.0g) added in one portion. The mixture was then stirred at room temperature with the exclusion of atmospheric moisture for 1h.

The resulting suspension was filtered through Celite and the filter pad washed several times with anhydrous tetrahydrofuran. Rotary evaporation of the combined filtrate and washings gave a gummy red solid which was washed with anhydrous ether to afford 6,7-dichloro-3,4-dihydro-3,4-dioxo-2-phenylquinoline 1-N-oxide (157b) as a red solid (65%), which formed red microcrystals, mp 228-230°C (from dimethylformamide), ν_{\max} 1706 and 1663 (C=O) cm^{-1} , $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.39 (1H, br s, ArH), 8.30 (1H, br s, ArH), and 7.51 (5H, s, ArH).

Found: C, 56.0; H, 2.1; N, 4.6%; $m/z(\text{EIMS})$, 323, 321, 319 (M^+).

$\text{C}_{15}\text{H}_7\text{Cl}_2\text{NO}_3$ requires: C, 56.3; H, 2.2; N, 4.4%; M, 320.

Reduction Reactions of 6-Chloro-3,4-dihydro-3,4-dioxo-2-phenylquinoline 1-N-oxides (157)

- (a) A solution of the corresponding 6-chloro-3,4-dihydro-3,4-dioxo-2-phenylquinoline 1-N-oxide (157) (0.001mol) in anhydrous 1,4-dioxane (10.0ml)

was hydrogenated over 10% palladium-on-charcoal (10% by weight) at room temperature and atmospheric pressure until no further hydrogen was absorbed.

The mixture was filtered through Celite and the filter pad was washed several times with anhydrous 1,4-dioxane. Rotary evaporation of the combined 1,4-dioxane filtrate and washings gave the crude 6-chloro-1,4-dihydro-1,3-dihydroxy-4-oxo-2-phenylquinoline derivative (152) which was purified as described for the individual reactions below.

- (i) 6-Chloro-3,4-dihydro-3,4-dioxo-7-methyl-2-phenylquinoline 1-N-oxide (157a) afforded 6-chloro-3,4-dihydro-1,3-dihydroxy-7-methyl-4-oxo-2-phenylquinoline (152a) as a beige solid (76%), which formed beige microcrystals, mp 260-262°C (from ethanol), identical (mp and IR spectrum) to a sample prepared before.
- (ii) 6,7-Dichloro-3,4-dihydro-3,4-dioxo-2-phenylquinoline 1-N-oxide (157b) afforded 6,7-dichloro-3,4-dihydro-1,3-dihydroxy-4-oxo-2-phenylquinoline (152b) as a beige solid (94%), mp 200-202°C, identified by comparison (mp and IR spectrum) with a sample prepared before.
- (b) A solution of the corresponding 6-chloro-1,3-dihydro-3,4-dioxo-2-phenylquinoline 1-N-oxide (157) (0.002mol) in 70% w/v aqueous ethanol (40ml) was treated with an equal weight of sodium dithionite, added in one portion and the mixture was stirred and heated under reflux for 0.5h. A second equal weight of sodium dithionite was then added and stirring and heating under reflux was continued for a further 0.5h.

The resulting suspension was rotary evaporated and the residue treated with water and the insoluble solid collected, washed with water, and dried *in vacuo* to afford the 6-chloro-1,4-dihydro-3-hydroxy-4-oxo-2-phenylquinoline derivative (158) which was purified as described for the individual reactions below.

- (i) 6-Chloro-3,4-dihydro-3,4-dioxo-7-methyl-2-phenylquinoline 1-N-oxide (157a) afforded 6-chloro-1,4-dihydro-3-hydroxy-7-methyl-4-oxo-2-phenylquinoline

(158a) as a pale yellow solid (82%), mp 286-289°C, identified by comparison (mp and IR spectrum) with a sample prepared before.

- (ii) 6,7-Dichloro-3,4-dihydro-3,4-dioxo-2-phenylquinoline 1-N-oxide (157b) afforded 6,7-dichloro-1,4-dihydro-3-hydroxy-4-oxo-2-phenylquinoline (158b) as a colourless solid (77%), which formed colourless microcrystals, mp 303-305°C (from glacial acetic acid), identified by comparison (mp and IR spectrum) with a sample prepared before.

6-Chloro-3,4-diethoxy-2-phenylquinolines (162)

A mixture of the corresponding 6-chloro-3,4-dihydro-3,4-dioxo-2-phenylquinoline 1-N-oxide derivative (157) (0.002mol) and triethyl phosphite (2.0ml; 0.012mol) was heated under reflux for 6h.

The resulting red solution was rotary evaporated under high vacuum (oil pump) and the residue was treated with water (10.0ml) and extracted several times with dichloromethane. Rotary evaporation of the combined dichloromethane extracts gave a yellow- brown oil which was purified by flash- chromatography in hexane- dichloromethane (1:1) over silica to give the corresponding 6-chloro-3,4-diethoxy-2-phenylquinoline derivative (162).

- (i) 6-Chloro-3,4-dihydro-3,4-dioxo-7-methyl-2-phenylquinoline 1-N-oxide (157a) afforded 6-chloro-3,4-diethoxy-7-methyl-2-phenylquinoline (162a) as a yellow oil (16%), bp 210°C/0.1mmHg which crystallised to give a yellow solid, mp 78-80°C, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.05 (1H, s, ArH), 7.94 (1H, s, ArH), 7.93-7.89 (2H, m, ArH), 7.52-7.48 (3H, m, ArH), 4.47 (2H, q, J 7.0, CH₂), 3.77 (2H, q, J 7.0, CH₂), 2.49 (3H, s, CH₃), 1.43 (3H, t, J 7.0, CH₃), and 1.11 (3H, t, J 7.0, CH₃).

Found: C, 70.1; H, 5.7; N, 4.1%; m/z(EIMS), 343, 341 (M⁺).

C₂₀H₂₀ClNO₂ requires: C, 70.3; H, 5.9; N, 4.1%; M, 341.5.

- (ii) 6,7-Dichloro-3,4-dihydro-3,4-dioxo-2-phenylquinoline 1-N-oxide (157b) gave 6,7-dichloro-3,4-diethoxy-2-phenylquinoline (162b) as a yellow oil (37%), bp 210°C/0.1mmHg which crystallised to a yellow solid, mp 72-74°C, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$

8.24 (1H, s, ArH), 8.23 (1H, s, ArH), 7.94-7.89 (2H, m, ArH), 7.55-7.48 (3H, m, ArH), 4.50 (2H, q, J 7.0, CH₂), 3.79 (2H, q, J 7.0, CH₂), 1.44 (3H, t, J 7.0, CH₃), and 1.11 (3H, t, J 7.0, CH₃), δ_c [(CD₃)₂SO] 157.9 (quat.), 152.2 (quat.), 143.9 (quat.), 141.8 (quat.), 137.2 (quat.), 131.7 (quat.), 130.0 (2 x CH), 129.3 (2 x CH), 128.1 (2 x CH), 123.7 (2 x quat.), 122.9 (CH), 69.7 (CH₂), 69.4 (CH₂), 15.7 (CH₃), and 15.2 (CH₃).

Found: C, 62.8; H, 4.8; N, 3.9%; m/z(EIMS), 365, 363, 361 (M⁺).

C₁₉H₁₇Cl₂NO₂ requires: C, 63.0; H, 4.7; N, 3.9%; M, 362.

6-Chloro-3,4-dihydro-3,4-dioxo-2-phenylquinolines (156)

A solution of the corresponding 6-chloro-1,4-dihydro-3-hydroxy-4-oxo-2-phenylquinoline derivative (158) (0.004mol) in anhydrous dimethylformamide (40.0ml) was stirred and treated at room temperature with activated manganese dioxide (Aldrich, 21,764-6) (2.0g) added in one portion. The resulting suspension was then stirred at room temperature for 2h.

The mixture was filtered through Celite and the filter pad washed several times with anhydrous dimethylformamide. Rotary evaporation of the combined dimethylformamide filtrate and washings gave a red oil which was purified by flash-chromatography over silica to give the individual 6-chloro-3,4-dihydro-3,4-dioxo-2-phenylquinolines (156) as described below.

- (i) Flash- chromatography of the red oil from 6-chloro-1,4-dihydro-3-hydroxy-7-methyl-4-oxo-2-phenylquinoline (158a) eluting with dichloromethane- ethyl acetate (1:1) gave 6-chloro-3,4-dihydro-3,4-dioxo-7-methyl-2-phenylquinoline (156a) as a red solid (26%), which formed red microcrystals, mp 123-125°C (from ethanol), ν_{\max} 1728 and 1709 (C=O) cm⁻¹, δ_H [(CD₃)₂SO] 8.26 (1H, d, J 1.5, ArH), 8.22 (1H, d, J 1.8, ArH), 7.61-7.50 (5H, m, ArH), and 2.41 (3H, s, CH₃).

Found: C, 67.9; H, 4.1; N, 5.2%; m/z(HRFABMS), 284.0472 [(M+H)⁺].

C₁₆H₁₀³⁵ClNO₂ requires: C, 67.7; H, 3.5; N, 4.9%; (M+H), 284.0478.

(ii) Flash- chromatography of the red oil from 6,7-dichloro-1,4-dihydro-3-hydroxy-4-oxo-2-phenylquinoline (158b) eluting with dichloromethane- ethyl acetate (1:1) gave 6,7-dichloro-3,4-dihydro-3,4-dioxo-2-phenylquinoline (156b) as a red solid (9%) which formed red microcrystals, mp 140-142°C (from light petroleum), ν_{\max} 1731 and 1676 (C=O) cm^{-1} , $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.28-8.25 (2H, m, ArH), 7.89 (1H, s, ArH), 7.85 (1H, s, ArH), and 7.75-7.53 (3H, m, ArH).

Found: C, 59.5; H, 2.4; N, 4.8%; m/z(EIMS), no parent ion.

$\text{C}_{15}\text{H}_7\text{Cl}_2\text{NO}_2$ requires: C, 59.2; H, 2.3; N, 4.6%; M, 304.

Further elution with dichloromethane- ethyl acetate (3:7) gave a viscous brown oil which was triturated with ether to afford unreacted starting material (158b) (13%), mp 290-293°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

Reactions of 6-Chloro-1,4-dihydro-1,3-dihydroxy-4-oxo-2-phenylquinolines (152) with Acetic Anhydride

(a) The corresponding 6-chloro-1,4-dihydro-1,3-dihydroxy-4-oxo-2-phenylquinoline derivative (152) (0.002mol) was treated with acetic anhydride (5.0ml) and the mixture was stirred and heated under reflux for 3h.

The resulting red solution was rotary evaporated under high vacuum (oil pump) and the oil obtained was flash- chromatographed over silica to give the corresponding 3-acetoxyquinoline derivative (159) as described for the individual reactions below.

(i) The red oil obtained from 6-chloro-1,4-dihydro-1,3-dihydroxy-7-methyl-4-oxo-2-phenylquinoline (152a) was flash- chromatographed over silica eluting with dichloromethane to afford 3-acetoxy-6-chloro-1,4-dihydro-7-methyl-4-oxo-2-phenylquinoline (159a) as a colourless solid (21%), which formed colourless microcrystals, mp 258-260°C (from ethanol- light petroleum), ν_{\max} 3059 (NH), and 1767 (C=O) cm^{-1} , $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 12.24 (1H, s, NH)(exch.), 8.22 (1H, s,

ArH), 7.96 (1H, s, ArH), 7.61 (5H, s, ArH), 2.46 (3H, s, CH₃), and 2.11 (3H, s, CH₃).

Found: m/z(HREIMS), 327.0666 (M⁺).

C₁₈H₁₄³⁵ClNO₃ requires: M, 327.0662.

- (ii) The red oil obtained from 6,7-dichloro-1,4-dihydro-1,3-dihydroxy-4-oxo-2-phenylquinoline (152b) was flash- chromatographed over silica eluting with dichloromethane to give 3-acetoxy-6,7-dichloro-1,4-dihydro-4-oxo-2-phenylquinoline (159b) as a light brown solid (33%), which formed beige microcrystals, mp 241-243°C (from ethyl acetate- light petroleum), ν_{\max} 3060 (NH), and 1769 and 1628 (C=O) cm⁻¹, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 12.24 (1H, s, NH)(exch.), 8.22 (1H, s, ArH), 7.96 (1H, s, ArH), 7.61 (5H, s, ArH), and 2.13 (3H, s, CH₃).

Found: m/z(HREIMS), 349.0078 (M⁺).

C₁₇H₁₁³⁵Cl³⁷ClNO₃ requires: M, 349.0087.

Found: m/z(HREIMS), 347.0118 (M⁺).

C₁₇H₁₁³⁵Cl³⁵ClNO₃ requires: M, 347.0116.

- (b) The corresponding 6-chloro-1,4-dihydro-1,3-dihydroxy-4-oxo-2-phenylquinoline (152) (0.001mol) was warmed at 100°C with acetic anhydride (0.4ml) for 10min then left at room temperature for 20min.

The resulting gummy red solid was triturated with ether to afford a red solid whose ¹H NMR spectrum showed it to be an inseparable mixture of 3-acetoxy-6-chloro-1,4-dihydro-4-oxo-2-phenylquinoline (159) and the 6-chloro-3,4-dihydro-3,4-dioxo-2-phenylquinoline 1-N-oxide (157).

- (i) 6-Chloro-1,4-dihydro-1,3-dihydroxy-7-methyl-4-oxo-2-phenylquinoline (152a) afforded a mixture of 3-acetoxy-6-chloro-1,4-dihydro-7-methyl-4-oxo-2-phenylquinoline (159a) and 6-chloro-3,4-dihydro-3,4-dioxo-7-methyl-2-phenylquinoline 1-N-oxide (157a) as an orange- red solid (0.4g) which formed

orange microcrystals, mp 184-186°C (from glacial acetic acid), ν_{\max} 2623 br (NH), and 1787 and 1705 (C=O) cm^{-1} , $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 12.20 (1H, br s, NH)(3-acetoxy), 8.22 (1H, d, J 0.6, ArH)(3-acetoxy), 8.05 (1H, s, ArH)(N-oxide), 8.02 (1H, s, ArH)(N-oxide), 7.70 (1H, d, J 0.6, ArH)(3-acetoxy), 7.59 (5H, s, ArH)(3-acetoxy), 7.51 (2H, s, ArH)(N-oxide), 7.51 (3H, s, ArH)(N-oxide), 2.54 (3H, s, CH_3)(3-acetoxy), 2.46 (3H, s, CH_3)(N-oxide), and 2.11 (3H, s, CH_3)(3-acetoxy).

(ii) 6,7-Dichloro-1,4-dihydro-1,3-dihydroxy-4-oxo-2-phenylquinoline (152b) afforded a mixture of 3-acetoxy-6,7-dichloro-1,4-dihydro-4-oxo-2-phenylquinoline (159b) and 6,7-dichloro-3,4-dihydro-3,4-dioxo-2-phenylquinoline 1-N-oxide (157b) as an orange-red solid (0.15g) which formed pale red microcrystals, mp 208-210°C (from ethanol- light petroleum), ν_{\max} 2584 br (NH), and 1783 and 1707 (C=O) cm^{-1} , $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 12.30 (1H, br s, NH)(exch.)(3-acetoxy), 8.40 (1H, s, ArH)(N-oxide), 8.28 (1H, s, ArH)(N-oxide), 8.20 (1H, s, ArH)(3-acetoxy), 8.00 (1H, s, ArH)(3-acetoxy), 7.60 (5H, s, ArH)(3-acetoxy), 7.52 (2H, s, ArH)(N-oxide), 7.52 (3H, s, ArH)(N-oxide), and 2.13 (3H, s, CH_3)(3-acetoxy).

(iii) 6-Chloro-1,4-dihydro-1,3-dihydroxy-7-nitro-4-oxo-2-phenylquinoline (152c) afforded a mixture of 3-acetoxy-6-chloro-1,4-dihydro-7-nitro-4-oxo-2-phenylquinoline (159c) and 6-chloro-3,4-dihydro-3,4-dioxo-7-nitro-2-phenylquinoline 1-N-oxide (157c) as an orange-red solid (0.28g) which formed pale red microcrystals, mp 220-222°C (from ethyl acetate- light petroleum), ν_{\max} 3082 (NH) and 1769 (C=O) cm^{-1} , $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 12.65 (1H, br s, NH)(3-acetoxy), 8.86 (1H, s, ArH)(N-oxide), 8.40 (2H, s, ArH)(3-acetoxy and N-oxide), 8.30 (1H, s, ArH)(3-acetoxy), 7.63 (5H, s, ArH)(3-acetoxy), 7.55 (3H, s, ArH)(N-oxide), 7.54 (2H, s, ArH)(N-oxide), and 2.15 (3H, s, CH_3)(3-acetoxy).

Reactions of 6-Chloro-1,4-dihydro-1,3-dihydroxy-7-nitro-4-oxo-2-phenylquinoline (152c) with Acetyl Chloride in the Presence of Triethylamine

(a) A solution of 6-chloro-1,4-dihydro-1,3-dihydroxy-7-nitro-4-oxo-2-phenylquinoline (152c) (0.33g; 0.001mol) in anhydrous 1,4-dioxane (3.0ml) was stirred and treated with triethylamine (0.125g; 0.17ml; 0.001mol) added in a single portion. The mixture was then treated dropwise with stirring at room temperature with a solution of acetyl chloride (0.085g; 0.011mol) in anhydrous 1,4-dioxane (2.0ml). The mixture was then stirred at room temperature with the exclusion of atmospheric moisture for 0.5h.

The resulting brown suspension was filtered to remove triethylamine hydrochloride and the 1,4-dioxane filtrate was rotary evaporated under high vacuum (oil pump). The residue was treated with water (2.5ml) and dichloromethane and the three phase mixture was filtered to afford 6-chloro-3,4-dihydro-3,4-dioxo-7-nitro-2-phenylquinoline 1-N-oxide (157c) as a red solid (0.11g; 33%), mp 238-240°C, which was identified by comparison (mp and IR spectrum) with a sample obtained before.

Rotary evaporation of the dichloromethane layer gave 3-acetoxy-6-chloro-1,4-dihydro-7-nitro-4-oxo-2-phenylquinoline (159c) as a light brown solid (0.07g; 19%), mp 219-221°C, ν_{\max} 3059 (NH), and 1769 (C=O) cm^{-1} .

Found: m/z (HREIMS), 360.0326 (M^+).

$C_{17}H_{11}^{37}ClN_2O_5$ requires: M , 360.0327.

Found: m/z (HREIMS), 358.0357 (M^+).

$C_{17}H_{11}^{35}ClN_2O_5$ requires: M , 358.0357.

(b) Repetition of the reaction described in (a) before but using two equivalents of triethylamine and acetyl chloride afforded the 1-N-oxide (157c) (15%) as the sole product, with no other identifiable material isolated.

The Reaction of 6-Chloro-1,4-dihydro-1,3-dihydroxy-7-methyl-4-oxo-2-phenylquinoline (152a) with Ethyl Chloroformate in the Presence of Triethylamine

A solution of the N-hydroxyquinoline derivative (152a) (0.3g; 0.001mol) in anhydrous dimethylformamide (5.0ml) was stirred and treated at room temperature with a solution of triethylamine (0.11g; 0.0011mol) in anhydrous dimethylformamide (2.5ml) added in one portion, followed dropwise with a solution of ethyl chloroformate (0.12g; 0.0011mol) in anhydrous dimethylformamide (2.5ml). The mixture was then stirred at room temperature with the exclusion of atmospheric moisture for 0.5h.

The red suspension was filtered to remove triethylamine hydrochloride and the dimethylformamide filtrate was rotary evaporated under high vacuum (oil pump). The residue obtained was treated with water and filtered to give a red solid which was flash- chromatographed over silica.

Elution with hexane-dichloromethane (3:7) gave 6-chloro-3,4-dihydro-3,4-dioxo-7-methyl-2-phenylquinoline 1-N-oxide (157a) as a red solid (0.18g; 60%), mp 204-206°C, which was identified by comparison (mp and IR spectrum) with a sample obtained before.

Further elution with dichloromethane-ethyl acetate (7:3) gave 6-chloro-1,4-dihydro-3-hydroxy-7-methyl-4-oxo-2-phenylquinoline (158a) as a light brown solid (0.1g; 35%), mp 290-292°C, which was identified by comparison (mp and IR spectrum) with a sample obtained before.

Reactions of 6-Chloro-1,4-dihydro-1,3-dihydroxy-4-oxo-2-phenylquinolines (152) with Toluene-4-sulfonyl Chloride in the Presence of Triethylamine

A solution of the corresponding N-hydroxyquinoline derivative (152) (0.001mol) in anhydrous dimethylformamide (5.0ml) was stirred and treated at room temperature with a solution of triethylamine (0.11g; 0.0011mol) in anhydrous dimethylformamide (2.5ml) added in one portion, followed dropwise with a solution of toluene-4-sulfonyl chloride (0.21g; 0.0011mol) in anhydrous dimethylformamide (2.5ml). The

mixture was then stirred at room temperature with the exclusion of atmospheric moisture for 0.5h.

The resulting suspension was filtered to remove triethylamine hydrochloride and the dimethylformamide filtrate was rotary evaporated under high vacuum (oil pump). The residue obtained was treated with water and filtered to give a red solid which was separated by flash- chromatography over silica as described for the individual reactions below.

- (i) Flash- chromatography of the red solid obtained from 6-chloro-1,4-dihydro-1,3-dihydroxy-7-methyl-4-oxo-2-phenylquinoline (152a) eluting with hexane-dichloromethane (3:7) gave 6-chloro-3,4-dihydro-3,4-dioxo-7-methyl-2-phenylquinoline 1-N-oxide (157a) as a red solid (33%), mp 204-206°C, which was identified by comparison (mp and IR spectrum) with a sample obtained before.

Further elution with dichloromethane- ethyl acetate (7:3) gave 6-chloro-1,4-dihydro-3-hydroxy-7-methyl-4-oxo-2-phenylquinoline (158a) as a light brown solid (60%), mp 287-290°C, which was identified by comparison (mp and IR spectrum) with a sample obtained before.

- (ii) Flash- chromatography of the red solid obtained from 6,7-dichloro-1,4-dihydro-1,3-dihydroxy-4-oxo-2-phenylquinoline (152b) eluting with hexane-dichloromethane (3:7) gave 6,7-dichloro-3,4-dihydro-3,4-dioxo-2-phenylquinoline 1-N-oxide (157b) as a red solid (19%), mp 225-228°C, which was identified by comparison (mp and IR spectrum) with a sample obtained before.

Further elution with dichloromethane- ethyl acetate (7:3) gave 6,7-dichloro-1,4-dihydro-3-hydroxy-4-oxo-2-phenylquinoline (158b) as a light brown solid (20%), mp 295-298°C, which was identified by comparison (mp and IR spectrum) with a sample obtained before.

The Attempted Reaction of 6,7-Dichloro-1,4-dihydro-1,3-dihydroxy-4-oxo-2-phenylquinoline (152b) with Concentrated Sulfuric Acid

The N-hydroxyquinoline derivative (152b) (0.32g; 0.001mol) was added in small portions with stirring at room temperature to concentrated sulfuric acid (1.0ml). The resulting red solution was then stirred at room temperature for 5min.

The red solution obtained was poured on to ice (5.0g) and the yellow suspension was filtered to give a pale yellow solid which was treated with 10% w/v aqueous sodium hydrogen carbonate solution (2.5ml). The resulting suspension was stirred at room temperature for 30min then filtered to afford the unreacted N-hydroxyquinoline derivative (152b) as a light brown solid (0.25g; 78%), mp 197-199°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

The Attempted Reaction of 6-Chloro-1,4-dihydro-1,3-dihydroxy-7-methyl-4-oxo-2-phenylquinoline (152a) with Ethanolic Sodium Ethoxide

A suspension of the N-hydroxyquinoline derivative (152a) (0.3g; 0.001mol) in anhydrous ethanol (5.0ml) was stirred and treated at room temperature with a solution of sodium (0.09g; 0.004g.atom) in anhydrous ethanol (5.0ml) added in one portion. The resulting suspension was then stirred and heated under reflux with the exclusion of atmospheric moisture for 0.5h.

The red solution was rotary evaporated and the residue was treated with water (5.0ml) and acidified with 2M aqueous hydrochloric acid. Filtration gave an intractable solid (0.25g) which yielded no identifiable material.

The Reaction of 6-Chloro-1,4-dihydro-1,3-dihydroxy-7-methyl-4-oxo-2-phenylquinoline (152a) with Triethylamine in Dimethylformamide

A solution of the N-hydroxyquinoline derivative (152a) (0.3g; 0.001mol) in anhydrous dimethylformamide (5.0ml) was stirred and treated at room temperature with a solution of triethylamine (0.11g; 0.0011mol) in anhydrous dimethylformamide (5.0ml) added in one portion. The mixture was then stirred at room temperature with the exclusion of atmospheric moisture for 0.5h.

The resulting red suspension was filtered to remove triethylamine hydrochloride and the dimethylformamide filtrate was rotary evaporated under high vacuum (oil pump). The residue was treated with water (5.0ml) and filtered to afford a light brown solid which was flash- chromatographed over silica.

Elution with hexane-dichloromethane (3:7) gave 6-chloro-3,4-dihydro-3,4-dioxo-7-methyl-2-phenylquinoline 1-N-oxide (157a) as a red solid (0.01g; 3%), mp 204-206°C, which was identified by comparison (mp and IR spectrum) with a sample obtained before.

Further elution with dichloromethane-ethyl acetate (7:3) gave 6-chloro-1,4-dihydro-3-hydroxy-7-methyl-4-oxo-2-phenylquinoline (158a) as a light brown solid (0.01g; 4%), mp 290-292°C, which was identified by comparison (mp and IR spectrum) with a sample obtained before.

The Reaction of 6-Chloro-1,4-dihydro-1,3-dihydroxy-7-methyl-4-oxo-2-phenylquinoline (152a) with Phenyl Isocyanate in Dimethylformamide

A solution of the N-hydroxyquinoline derivative (152a) (0.3g; 0.001mol) in dimethylformamide (15.0ml) was stirred and treated at room temperature with a solution of phenyl isocyanate (0.12g; 0.001mol) in anhydrous dimethylformamide (5.0ml) added in one portion. The mixture was then stirred at room temperature with the exclusion of atmospheric moisture for 30min.

The red solution was rotary evaporated and the viscous red oil obtained was triturated with methanol to afford the quinoline 1-N-oxide derivative (157a) as a red solid (0.06g; 20%), mp 202-205°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

The Reaction of *Trans* 2-Benzoyl-3-(4-methyl-2-nitrophenyl)oxirane (149a) with Hydrogen Chloride in the Presence of Hydroquinone

A solution of the *trans* oxirane derivative (149a) (1.1g; 0.004mol) in anhydrous 1,4-dioxane (25.0ml) was treated with a solution of hydroquinone (0.44g; 0.004mol) in anhydrous 1,4-dioxane (25.0ml) and the mixture was stirred and cooled to 11°C (ice-

water bath), then treated with a slow stream of hydrogen chloride until saturated. The mixture was securely stoppered and stored in a fridge for 19h.

The resulting yellow solution was rotary evaporated and the gummy orange solid obtained was triturated with ether to afford a solid (0.6g), flash- chromatography of which over silica yielded no identifiable material.

Rotary evaporation of the ethereal mother liquor gave a red oil (0.7g) which was treated with 10% w/v aqueous sodium hydrogen carbonate (5.0ml) and extracted several times with dichloromethane. Rotary evaporation of the dichloromethane extracts gave a red oil which was flash- chromatographed over silica.

Elution with hexane-dichloromethane (2:3) gave 1-phenyl-3-(4-methyl-2-nitrophenyl)propane-1,2-dione (151a) as a yellow solid (0.23g; 20%), mp 63-66°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

The Reaction of *Trans* 2-Benzoyl-3-(4-methyl-2-nitrophenyl)oxirane (149a) with Hydrogen Chloride in the Presence of Benzyltriethylammonium Chloride

A solution of the *trans* oxirane derivative (149a) (0.56g; 0.002mol) in anhydrous dichloromethane (20.0ml) was stirred and treated with benzyltriethylammonium chloride added in one portion. The resulting solution was stirred and cooled to 0°C (ice- salt bath) then treated with a slow stream of hydrogen chloride until saturated. The mixture was then securely stoppered and stored in a fridge for 19h.

The resulting orange- red solution was rotary evaporated and the red oil obtained was treated with water (5.0ml) then extracted several times with dichloromethane to give a red oil, flash- chromatography of which over silica yielded no identifiable material.

The Reaction of *Trans* 2-Benzoyl-3-(4-methyl-2-nitrophenyl)oxirane (149a) with Hydrogen Chloride in the Presence of Boron Trifluoride Etherate

A solution of the *trans* oxirane derivative (149a) (1.1g; 0.004mol) in anhydrous 1,2-dimethoxyethane (30.0ml) was stirred and cooled to 0°C (ice- salt bath), then treated with a solution of boron trifluoride etherate (2.4g; 2.0ml; 0.016mol) in anhydrous 1,2-dimethoxyethane (10.0ml), added in one portion. The mixture was treated at 0°C

with stirring with a slow stream of hydrogen chloride until saturated. The mixture was then securely stoppered and stored in a fridge for 19h.

The resulting orange- red solution was rotary evaporated and the residual red oil was cautiously treated with ice (20g), followed dropwise with 10% w/v aqueous sodium hydrogen carbonate solution until basic. Extraction with dichloromethane gave a red oil which was triturated with ether- ethyl acetate to afford a red solid. This was flash- chromatographed over silica.

Elution with hexane-dichloromethane (1:9) gave 6-chloro-3,4-dihydro-3,4-dioxo-7-methyl-2-phenylquinoline 1-N-oxide (157a) as a red solid (0.16g; 13%), mp 215-217°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

Rotary evaporation of the ether-ethyl acetate mother liquor gave a red oil, flash- chromatography of which over silica yielded no identifiable material.

The Attempted Reaction of 2,2-Dibenzoyl-3-(4-chloro-2-nitrophenyl)oxirane (164b; $R^1=R^2=Ph$) with Hydrogen Chloride

A solution of the oxirane derivative (164b; $R^1=R^2=Ph$) (0.81g; 0.002mol) in anhydrous 1,4-dioxane (20.0ml) was stirred and cooled to 11°C (ice- salt bath) then treated with a slow stream of hydrogen chloride until saturated. The resulting yellow solution was securely stoppered and stored in a fridge for 72h.

The yellow solution was rotary evaporated and the residual orange- red oil was treated with 10% w/v aqueous sodium hydrogen carbonate solution (2.5ml) then extracted several times with dichloromethane. Rotary evaporation of the combined dichloromethane extracts gave a red oil (0.81g) flash- chromatography of which yielded no identifiable material.

The Attempted Reaction of *Trans* 2-Benzoyl-3-(4-methyl-2-nitrophenyl)oxirane (149a) with Aluminium Trichloride in Dichloromethane

A suspension of aluminium trichloride (0.55g; 0.004mol) in anhydrous dichloromethane (10.0ml) was stirred and cooled to -10°C (ice- acetone bath) then

treated dropwise with a solution of the oxirane derivative (149a) (0.57g; 0.002mol) in anhydrous dichloromethane (10.0ml). The mixture was then stirred at room temperature under nitrogen for 4h.

The resulting dark red- brown suspension was stirred and treated slowly with 10% w/v aqueous sodium hydrogen carbonate solution (30.0ml) and the mixture then stirred at room temperature for 15min. The three phase mixture obtained was filtered to remove inorganic material and the aqueous- dichloromethane filtrate was separated and the aqueous layer extracted several times with dichloromethane. Rotary evaporation of the combined dichloromethane extracts gave only an intractable brown solid (0.2g) whose TLC in dichloromethane over silica showed it to be a multicomponent mixture which was not further investigated.

1-N-(1-Benzoyl-1-hydroxy)methyl-1,3-dihydro-3-oxo-2,1-benzisoxazoles (169)

(a) A solution of the corresponding 2-benzoyl-3-(2-nitrophenyl)oxirane derivative (149) or (150) (0.002mol) in anhydrous toluene (16.0ml) was stirred and treated dropwise at room temperature with a solution of stannic chloride (0.56g; 0.0022mol) in anhydrous toluene (4.0ml). The mixture was then stirred at room temperature with the exclusion of atmospheric moisture for 15min.

The resulting suspension was poured on to ice (20.0g) and the toluene layer separated. The aqueous layer was extracted several times with dichloromethane, the combined toluene- dichloromethane extracts were rotary evaporated and the oily solid obtained purified as described for the individual reactions below.

(i) The oily solid from *trans* 2-benzoyl-3-(4-methyl-2-nitrophenyl)oxirane (149a) was triturated with ether to afford 1-N-(1-benzoyl-1-hydroxy)methyl-1,3-dihydro-6-methyl-3-oxo-2,1-benzisoxazole (169a) as a pink solid (87%), which formed colourless microcrystals, mp 135-137°C (from ethanol), ν_{\max} 3437 (OH), and 1764, 1746 and 1691 (C=O) cm^{-1} , $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.23 (1H, s, ArH), 8.20 (1H, s, ArH), 7.71-7.68 (3H, m, ArH), 7.63-7.56 (2H, m, ArH), 7.22 (1H, d, J 8.3, ArH), 7.16 (1H, d, J 9.7, OH)(exch.), 7.00 (1H, s, CH), and 2.50 (3H, s, CH₃).

Found: C, 67.8; H, 4.6; N, 4.9%; m/z (HRFABMS), 284.0928 [(M+H)⁺].
C₁₆H₁₃NO₄ requires: C, 67.8; H, 4.6; N, 4.9%; (M+H), 284.0923.

- (ii) The oily solid from *trans* 2-benzoyl-3-(4-chloro-2-nitrophenyl)oxirane (149b) was triturated with ether to afford 1-N-(1-benzoyl-1-hydroxy)methyl-6-chloro-1,3-dihydro-3-oxo-2,1-benzisoxazole (169b) as a cream coloured unstable hydrochloride salt, mp 228-230°C, ν_{\max} 3442 (OH or NH⁺), and 1764 and 1688 (C=O) cm⁻¹, which on heating in ethanol for 30min was converted into 6-chloro-1-N-(1-benzoyl-1-hydroxy)methyl-3-oxo-2,1-benzisoxazole (169b), obtained as a light brown solid (63%), which formed colourless microcrystals, mp 142-144°C (from ethanol), ν_{\max} 3418 (OH), and 1769 and 1692 (C=O) cm⁻¹, δ_H [(CD₃)₂SO] 8.22-8.21 (1H, m, ArH), 8.18-8.16 (2H, m, ArH), 7.85 (1H, dd, J 8.4 and 0.4, ArH), 7.71-7.68 (1H, m, ArH), 7.67-7.59 (2H, m, ArH), 7.44 (1H, dd, J 8.4 and 1.7, ArH), 7.35 (1H, d, J 9.5, OH)(exch.), and 7.03 (1H, d, J 9.5, CH).

Found: C, 59.0; H, 3.3; N, 4.6%; m/z (FABMS), 306, 304 [(M+H)⁺].
C₁₅H₁₀ClNO₄ requires: C, 59.3; H, 3.3; N, 4.6%; M, 303.5.

- (b) The reaction conditions described in (a) before were repeated but using anhydrous dichloromethane in place of anhydrous toluene as solvent. The mixture was worked up as described before and the oily solid product obtained was purified as described for the individual reactions below.

- (i) The oily solid from *trans* 2-benzoyl-3-(4-methyl-2-nitrophenyl)oxirane (149a) was flash- chromatographed over silica, eluting with hexane-dichloromethane (1:9) to give 1-N-(1-benzoyl-1-hydroxy)methyl-1,3-dihydro-6-methyl-3-oxo-2,1-benzisoxazole (169a) as a pink solid (30%), mp 130-133°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

- (ii) The gummy brown solid obtained from *cis* 1-benzoyl-2-(4-methyl-2-nitrophenyl)oxirane (150a) was flash- chromatographed over silica.

Elution with hexane-dichloromethane (1:1) gave 1-N-(1-benzoyl-1-hydroxy)methyl-1,3-dihydro-6-methyl-3-oxo-2,1-benzisoxazole (169a) as a light brown solid (30%), mp 133-135°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

Further elution with hexane-dichloromethane (1:1) gave 2-N-(1,2-dioxo-1-phenyl)ethylamino-4-methylbenzoic acid (170a) as a beige solid (55%), which formed colourless microcrystals, mp 210-212°C (from ethyl acetate- light petroleum), ν_{\max} 3500-2250 br (OH and NH), and 1681 (C=O) cm^{-1} , $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 12.45 (1H, s, OH or NH)(exch.), 8.51 (1H, s, ArH), 8.22 (2H, d, J 7.3, ArH), 7.94 (1H, d, J 8.0, ArH), 7.76-7.69 (1H, m, ArH), 7.60-7.53 (2H, m, ArH), 7.06 (1H, d, J 8.1, ArH), and 2.39 (3H, s, CH_3).

Found: C, 67.6; H, 4.5; N, 4.9%; m/z (FABMS), 284 $[(\text{M}+\text{H})^+]$.

$\text{C}_{16}\text{H}_{13}\text{NO}_4$ requires: C, 67.8; H, 4.6; N, 4.9%; M, 283.

- (iii) The gummy light brown solid from *trans* 2-benzoyl-3-(4-chloro-2-nitrophenyl)oxirane (149b) was triturated with ether to afford 1-N-(1-benzoyl-1-hydroxy)methyl-6-chloro-1,3-dihydro-3-oxo-2,1-benzisoxazole (169b) as a cream coloured, unstable hydrochloride salt, mp 213-215°C, identified by comparison (IR spectrum) with a sample obtained before. Brief heating of the hydrochloride in ethanol converted it into 1-N-(1-benzoyl-1-hydroxy)methyl-6-chloro-1,3-dihydro-3-oxo-2,1-benzisoxazole (169b), obtained as a light brown solid (66%), mp 138-140°C, identified by comparison (mp and IR spectrum) with a sample obtained before.
- (iv) The gummy yellow- brown solid from *trans* 2-benzoyl-3-(2,4-dinitrophenyl)oxirane (149c) was triturated with ether to afford 1-N-(1-benzoyl-1-hydroxy)methyl-1,3-dihydro-6-nitro-3-oxo-2,1-benzisoxazole (169c) as a beige solid (60%), which formed pale yellow microcrystals, mp 131-133°C (from ethanol), ν_{\max} 3413 (OH), 1767 and 1691 (C=O), and 1532 and 1345 (NO_2) cm^{-1} , $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.98-8.97 (1H, m, ArH), 8.26-8.21 (2H,

m, ArH), 8.20-8.05 (2H, m, ArH), 7.75-7.69 (2H, m, ArH), 7.63 (1H, s, OH)(exch.), 7.60-7.56 (1H, m, ArH), and 7.24 (1H, s, CH).

Found: C, 56.6; H, 3.1; N, 9.0%; m/z(FABMS), 180 [(M-PhCOCHO)⁺].

C₁₅H₁₀N₂O₆ requires: C, 57.3; H, 3.2; N, 8.9%; M, 314.

The Attempted Reaction of 1-N-(1-Benzoyl-1-hydroxy)methyl-1,3-dihydro-6-methyl-3-oxo-2,1-benzisoxazole (169a) with Silicagel in Dichloromethane

A solution of the isoxazole derivative (169a) (0.57g; 0.002mol) in dichloromethane (20.0ml) was stirred and treated with silicagel (2.0g) and the suspension stirred at room temperature for 1h.

The brown suspension was filtered and the dichloromethane filtrate was rotary evaporated to give unreacted starting material (169a) as a light brown solid (0.52g; 91%), mp 134-136°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

Reactions of 1-N-(1-Benzoyl-1-hydroxy)methyl-1,3-dihydro-3-oxo-2,1-benzisoxazoles (169) with Acetic Anhydride

The corresponding 1-N-(1-benzoyl-1-hydroxy)methyl-1,3-dihydro-3-oxo-2,1-benzisoxazole derivative (169) (0.002mol) was treated with acetic anhydride (5.0ml) and the mixture stirred and heated under reflux with the exclusion of atmospheric moisture for 3h.

The resulting brown solution was rotary evaporated under high vacuum (oil pump) to give a brown oil which was purified as described for the individual reactions below.

- (i) The brown oil obtained from 1-N-(1-benzoyl-1-hydroxy)methyl-1,3-dihydro-6-methyl-3-oxo-2,1-benzisoxazole (169a) was flash- chromatographed over silica.

Elution with hexane-dichloromethane (2:3) afforded 2-benzoyl-7-methyl-4-oxo-4H-3,1-benzoxazine (171a) as a light brown solid (0.2g; 38%), which formed colourless microcrystals, mp 171-173°C (from ethanol), ν_{\max} 1753 and 1667

(C=O) cm^{-1} , $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.22-8.18 (2H, m, ArH), 8.11 (1H, d, J 7.9, ArH), 7.76-7.71 (1H, m, ArH), 7.63-7.55 (4H, m, ArH), and 2.50 (3H, s, CH_3).

Found: C, 72.2; H, 3.9; N, 5.2%; $m/z(\text{EIMS})$, 265 (M^+).

$\text{C}_{16}\text{H}_{11}\text{NO}_3$ requires: C, 72.5; H, 4.2; N, 5.3%; M, 265.

(ii) The brown oil obtained from 1-N-(1-benzoyl-1-hydroxy)methyl-6-chloro-1,3-dihydro-3-oxo-2,1-benzisoxazole (169b) was triturated with ether to afford 2-benzoyl-7-chloro-4-oxo-4H-3,1-benzoxazine (171b) as a brown solid (0.35g; 61%), which formed brown microcrystals, mp 137-139°C (from ethyl acetate-light petroleum), ν_{max} 1768 and 1672 ($\text{C}=\text{O}$) cm^{-1} , $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.25-8.19 (2H, m, ArH), 7.95 (1H, d, J 1.9, ArH), 7.85-7.73 (3H, m, ArH), and 7.64-7.57 (2H, m, ArH).

Found: C, 62.5; H, 2.9; N, 4.7%.

$\text{C}_{15}\text{H}_8\text{ClNO}_3$ requires: C, 63.0; H, 3.2; N, 4.9%.

Found: $m/z(\text{HREIMS})$, 287.0167 (M^+).

$\text{C}_{15}\text{H}_8^{37}\text{ClNO}_3$ requires: M, 287.0163.

Found: $m/z(\text{HREIMS})$, 285.0188 (M^+).

$\text{C}_{15}\text{H}_8^{35}\text{ClNO}_3$ requires: M, 285.0193.

Attempted Solvolysis Reactions of 1-N-(1-Benzoyl-1-hydroxy)methyl-1,3-dihydro-6-methyl-3-oxo-2,1-benzisoxazole (169a)

(a) The benzisoxazole derivative (169a) (0.28g; 0.001mol) was gently warmed with 2M aqueous sodium hydroxide solution (2.5ml) until all of the suspended solid had dissolved.

The resulting orange solution was acidified with 2M aqueous hydrochloric acid and extracted several times with dichloromethane to give a red oil (0.18g), flash-chromatography of which over silica afforded no identifiable material.

- (b) A solution of the benzisoxazole derivative (169a) (1.1g; 0.004mol) in anhydrous ethanol (10.0ml) was mixed with a solution of sodium (0.37g; 0.016g.atom) in anhydrous ethanol (10.0ml) and the resulting red solution was stirred and heated under reflux with the exclusion of atmospheric moisture for 30min.

Work up of the resulting dark red solution gave no identifiable material.

Attempted Reduction Reactions of 1-N-(1-Benzoyl-1-hydroxy)methyl-1,3-dihydro-6-methyl-3-oxo-2,1-benzisoxazole (169a)

- (a) The benzisoxazole derivative (169a) (0.56g; 0.002mol) was hydrogenated in anhydrous 1,4-dioxane (20.0ml) over palladium-on-charcoal (0.06g) at room temperature and atmospheric pressure until no further hydrogen was absorbed.

The mixture was filtered through Celite and the pad washed several times with small portions of 1,4-dioxane. Rotary evaporation of the combined 1,4-dioxane filtrate and washings gave an orange oil which was triturated with ether to afford the unreacted starting material (169a) as an orange solid (0.3g; 54%), mp 134-136°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

Work up of the ethereal mother liquor gave no other identifiable material.

- (b) Repetition of the reaction described in (a) before but in glacial acetic acid, rather than 1,4-dioxane, as solvent, afforded after work up no identifiable material.
- (c) Repetition of the reaction described in (a) before but using Raney nickel (0.12g) as the catalyst and in glacial acetic acid as solvent gave after work up no identifiable material.
- (d) A solution of the benzisoxazole derivative (169a) (0.57g; 0.002mol) in 1,2-dimethoxyethane (10.0ml) was stirred and treated dropwise over 15min with a solution of sodium borohydride (0.38g; 0.01mol) in water (5.0ml). The mixture was then stirred at room temperature for 5h.

Work up of the mixture gave no identifiable material.

The Attempted Oxidation of 1-N-(1-Benzoyl-1-hydroxy)methyl-1,3-dihydro-6-methyl-3-oxo-2,1-benzisoxazole (169a) with Manganese Dioxide in 1,2-Dimethoxyethane

A solution of the benzisoxazole derivative (169a) (0.57g; 0.002mol) in anhydrous 1,2-dimethoxyethane (10.0ml) was stirred and treated at room temperature with activated manganese dioxide (Aldrich 21,764-6) (1.0g) added in one portion. The suspension was then stirred at room temperature with the exclusion of atmospheric moisture for 0.5h.

The suspension was filtered through Celite and the filter pad washed several times with small portions of 1,2-dimethoxyethane. Rotary evaporation of the combined 1,2-dimethoxyethane filtrate and washings gave a red oil which was flash-chromatographed over silica.

Elution with hexane-dichloromethane (2:3) gave impure 2-N-(1,2-dioxo-2-phenyl)ethylamino-4-methylbenzoic acid (170a) as a yellow solid (0.1g; 18%), mp 145-147°C, identified by comparison (mp and IR and ¹H NMR spectra) with a sample obtained before.

Further elution with dichloromethane through ether and ethyl acetate to methanol gave no other identifiable material.

Reactions of 2-Benzoyl-3-(2-nitrophenyl)oxiranes (149) and (150) with Boron Trifluoride Etherate in 1,2-Dimethoxyethane

A solution of the corresponding 2-benzoyl-3-(2-nitrophenyl)oxirane derivative (149) or (150) (0.01mol) in anhydrous 1,2-dimethoxyethane (75.0ml) was stirred and treated dropwise at room temperature with a solution of boron trifluoride etherate (6.0g; 5.0ml; 0.04mol) in anhydrous 1,2-dimethoxyethane (25.0ml). After the addition was complete the mixture was stirred and heated under reflux with the exclusion of atmospheric moisture for 15min.

The resulting dark red solution was poured carefully on to ice (100g) and the mixture extracted several times with dichloromethane to give a gummy red- brown solid

which was purified by flash- chromatography over silica as described for the individual reactions below.

(i) Flash- chromatography of the gummy solid product from *trans* 2-benzoyl-3-(4-methyl-2-nitrophenyl)oxirane (149a) eluting with hexane-dichloromethane (1:4) gave 2-N-(1,2-dioxo-2-phenyl)ethylamino-4-methylbenzoic acid (170a) as a light brown solid (52%), mp 210-212°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

(ii) Flash- chromatography of the gummy solid product from *cis* 2-benzoyl-3-(4-methyl-2-nitrophenyl)oxirane (150a) eluting with hexane-dichloromethane (1:1) gave 1-N-(1-benzoyl-1-hydroxy)methyl-1,3-dihydro-6-methyl-3-oxo-2,1-benzisoxazole (169a) as a brown solid (9%), mp 134-136°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

Further elution with hexane-dichloromethane (1:1) gave 2-N-(1,2-dioxo-2-phenyl)ethylamino-4-methylbenzoic acid (170a) as a light brown solid (71%), mp 208-210°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

(iii) Flash- chromatography of the gummy solid from *trans* 2-benzoyl-3-(4-chloro-2-nitrophenyl)oxirane (149b) eluting with hexane-dichloromethane (3:7) gave 6-chloro-1-N-(1-benzoyl-1-hydroxy)methyl-3-oxo-2,1-benzisoxazole (169b) as a colourless solid (33%), mp 138-140°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

Further elution with dichloromethane- ethyl acetate (4:1) gave 4-chloro-2-N-(1,2-dioxo-2-phenyl)ethylaminobenzoic acid (170b) as a light brown solid (21%), which formed pale yellow microcrystals, mp 220-222°C (from ethanol-light petroleum), ν_{\max} 3590 and 3489 (NH), 3300-2300 br (OH), and 1676 (C=O) cm^{-1} , $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 12.57 (1H, s, NH), 8.74 (1H, d, J 2.1, ArH), 8.24-8.20 (2H, m, ArH), 8.06 (1H, d, J 8.5, ArH), 7.80-7.70 (1H, m, ArH), 7.62-7.54 (2H, m, ArH), 7.34 (1H, dd, J 8.5 and 2.2, ArH), and 3.82 (1H, br s, OH).

Found: C, 58.5; H, 3.0; N, 4.8%.

C₁₅H₁₀ClNO₄ requires: C, 59.3; H, 3.3; N, 4.6%.

Found: m/z(HREIMS), 305.0276 (M⁺).

C₁₅H₁₀³⁷ClNO₄ requires: M, 305.0269.

Found: m/z(HREIMS), 303.0303 (M⁺).

C₁₅H₁₀³⁵ClNO₄ requires: M, 303.0298.

- (iv) Flash- chromatography of the gummy solid product from *trans* 1-benzoyl-2-(2,4-dinitrophenyl)oxirane (149c) eluting with hexane-dichloromethane (3:7) gave 1-N-(1-benzoyl-1-hydroxy)methyl-1,3-dihydro-6-nitro-3-oxo-2,1-benzisoxazole (169c) as a yellow solid (53%), mp 126-129°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

4-Oxo-4H-3,1-benzoxazine Derivatives (171)

The corresponding 2-N-(1,2-dioxo-2-phenyl)ethylaminobenzoic acid derivative (170) (0.002mol) was treated with acetic anhydride (5.0ml) and the mixture was heated under reflux with the exclusion of atmospheric moisture for 3h.

The resulting dark red solution was rotary evaporated under high vacuum (oil pump) and the brown oil obtained triturated with anhydrous ether to afford the corresponding 3,1-benzoxazine derivative (171) which was characterised as described for the individual reactions below.

- (i) 2-N-(1,2-Dioxo-2-phenyl)ethylamino-6-methylbenzoic acid (170a) gave 2-benzoyl-7-methyl-4-oxo-4H-3,1-benzoxazine (171a) as a brown solid (68%), mp 167-169°C, which was identified by comparison (mp and IR spectrum) with a sample obtained before.
- (ii) 6-Chloro-2-N-(1,2-dioxo-2-phenyl)ethylaminobenzoic acid (170b) gave 2-benzoyl-7-chloro-4-oxo-4H-3,1-benzoxazine (171b) as a brown solid (32%), mp 128-131°C, which was identified by comparison (mp and IR spectrum) with a sample obtained before.

The Boron Trifluoride Etherate Catalysed Rearrangement of the 2,1-Benzisoxazole Derivative (169a) to the Anthranilic Acid Derivative (170a)

A solution of the 2,1-benzisoxazole derivative (169a) (0.57g; 0.002mol) in anhydrous 1,2-dimethoxyethane (15.0ml) was stirred and treated dropwise at room temperature with a solution of boron trifluoride etherate (1.2g; 1.0ml; 0.008mol) in anhydrous 1,2-dimethoxyethane (5.0ml). The mixture was then stirred and heated under reflux with the exclusion of atmospheric moisture for 15min.

The resulting brown solution was poured on to ice (20.0g) and the mixture extracted several times with dichloromethane to give a gummy brown solid. This was purified by flash- chromatography in hexane-dichloromethane (1:1) over silica to afford 2-N-(1,2-dioxo-2-phenyl)ethylamino-4-methylbenzoic acid (170a) as a beige solid (0.38g; 67%), mp 208-210°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

The Attempted Reaction of *Trans* 2-Benzoyl-3-(4-methyl-2-nitrophenyl)oxirane (149a) with Boron Trichloride in Dichloromethane

A solution of the oxirane derivative (149a) (0.57g; 0.002mol) in anhydrous dichloromethane (5.0ml) was stirred under nitrogen and cooled to -10°C (ice- salt bath) then treated dropwise with a 1.0M solution of boron trichloride in anhydrous dichloromethane (2.0ml; 0.002mol) in anhydrous dichloromethane (8.0ml). The mixture was then stirred under nitrogen at -10°C for 2h.

The resulting orange- red solution was poured into 10% w/v aqueous sodium hydrogen carbonate solution (16.0ml; 0.02mol) and stirred at room temperature for 15min. The mixture was extracted several times with dichloromethane to give a red oil which was triturated with ether to afford the unreacted oxirane (149a) as an orange solid (0.3g; 53%), mp 114-116°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

Work up of the ethereal mother liquor afforded no other identifiable material.

The Reaction of *Trans* 2-Benzoyl-3-(4-methyl-2-nitrophenyl)oxirane (149a) with Boron Tribromide

A solution of the oxirane derivative (149a) (0.57g; 0.002mol) in anhydrous dichloromethane (5.0ml) was stirred under nitrogen and cooled to -10°C (ice- salt bath) then treated dropwise with a 1.0M solution of boron tribromide in anhydrous dichloromethane (2.0ml; 0.002mol) in anhydrous dichloromethane (8.0ml). The mixture was then stirred under nitrogen at -10°C for 2h.

The resulting orange- red solution was poured into 10% w/v aqueous sodium hydrogen carbonate solution (16.0ml; 0.02mol) and stirred at room temperature for 15min. The mixture was extracted several times with dichloromethane to give a red oil which was purified by flash- chromatography in hexane-dichloromethane (3:2) over silica to afford 3-bromo-1-phenyl-3-(4-methyl-2-nitrophenyl)propane-1,2-dione (172) as a yellow solid (0.13g; 18%) which formed yellow microcrystals, mp $76-78^{\circ}\text{C}$ (from light petroleum), ν_{max} 1722 and 1673 ($\text{C}=\text{O}$), and 1561 and 1377 (NO_2) cm^{-1} , $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.02-7.96 (3H, m, ArH), 7.89-7.71 (3H, m, ArH), 7.65-7.58 (2H, m, ArH), 7.19 (1H, s, CH), and 2.43 (3H, s, CH_3).

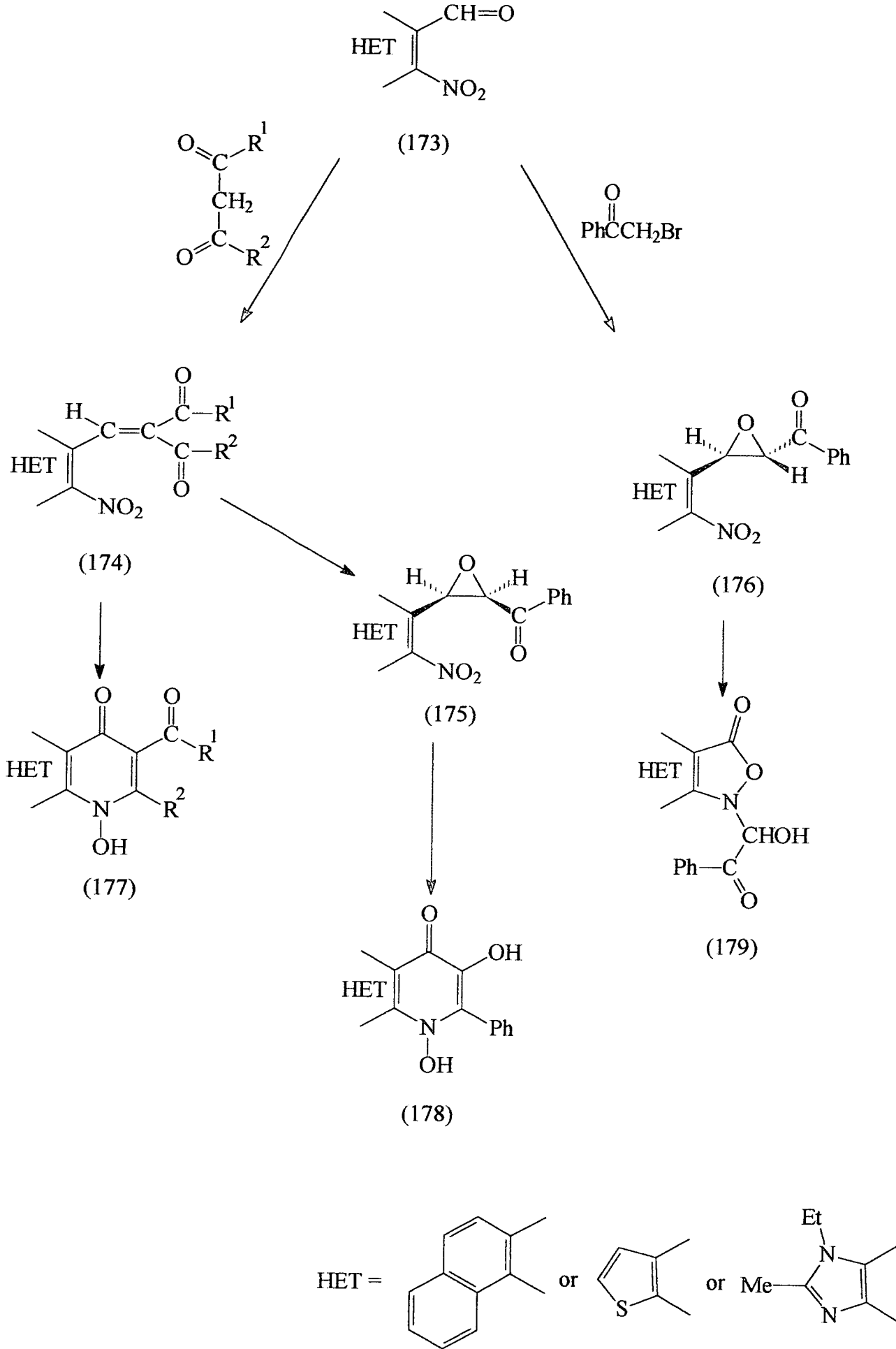
Found: C, 52.8; H, 3.3; N, 3.8%; $m/z(\text{FABMS})$, 364, 362 $[(\text{M}+\text{H})^+]$.

$\text{C}_{16}\text{H}_{12}\text{BrNO}_4$ requires: C, 53.0; H, 3.3; N, 3.9%; M, 362.

Further elution with dichloromethane through ethyl acetate to methanol gave no other identifiable material.

CHAPTER 3

STUDIES ON THE SYNTHESIS OF N-HYDROXY
BENZOQUINOLINONES, THIENOPYRIDINONES, AND
IMIDAZOPYRIDINONES BY ACID- CATALYSED CYCLISATION
REACTIONS OF SUBSTITUTED NITRONAPHTHALENE,
NITROTHIOPHENE AND NITROIMIDAZOLE DERIVATIVES



[R¹, R² = alkyl or aryl]

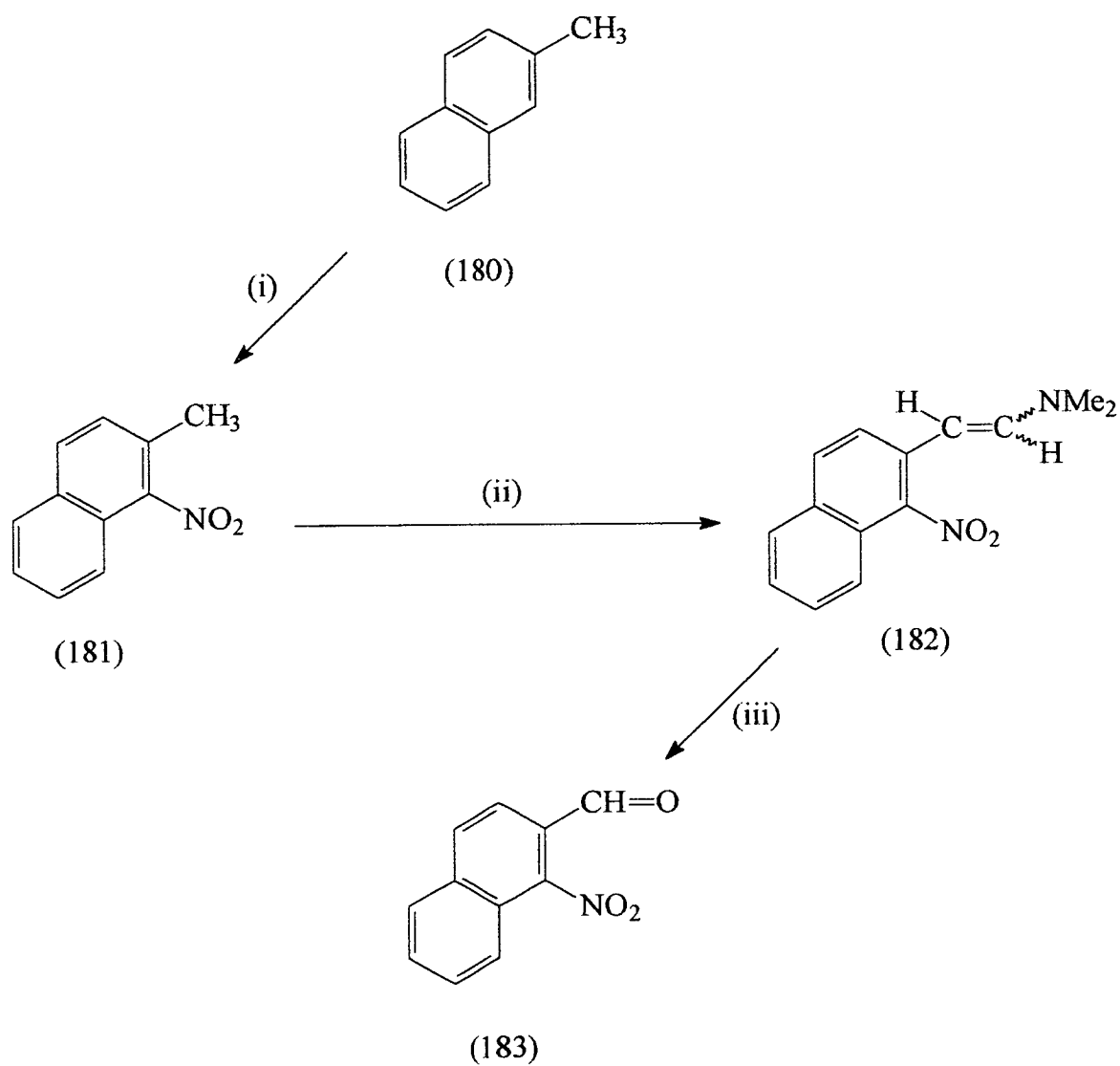
Scheme 39

STUDIES ON THE SYNTHESIS OF N-HYDROXY BENZOQUINOLINONES,
THIENOPYRIDINONES, AND IMIDAZOPYRIDINONES BY ACID-
CATALYSED CYCLISATION REACTIONS OF SUBSTITUTED
NITRONAPHTHALENE, NITROTHIOPHENE AND NITROIMIDAZOLE
DERIVATIVES

1. INTRODUCTION

As already discussed in Chapter 1 (see section 3.2, page 18 and Scheme 20), substituted 2-nitrobenzene derivatives undergo acid- catalysed cyclisation to afford N-hydroxyquinolinones. The studies described in the present Chapter extend the 2-nitrobenzene based cyclisation reactions reported in Chapter 2 to the syntheses of otherwise inaccessible N-hydroxybenzoquinolinones, thienopyridinones, and imidazopyridinones by the acid- catalysed cyclisation reactions of ortho substituted nitronaphthalene, nitrothiophene and nitroimidazole derivatives. These investigations (Scheme 39) are discussed under three main headings corresponding to the synthesis of fused heterocycles of the general structural types (177), (178) or (179).

Initially studies exploring the acid- catalysed cyclisation reactions of nitronaphthylidene, nitrothienylidene and imidazolylidene derivatives (174) [derived from the corresponding 2-nitroaromatic aldehyde (173)] to the corresponding fused N-hydroxypyridinone (177) are described. The acid catalysed cyclisation reactions of the *cis* acyl oxirane derivatives (175) to give fused 1,3-dihydroxypyridinone heterocycles (178) are next described, followed by investigations of the Lewis acid catalysed cyclisation reactions of nitronaphthyl, nitrothienyl, and nitroimidazolyl oxirane derivatives (176) to the corresponding naphthisoxazolone, thienoisoxazole and imidazoisoxazole derivatives (179).

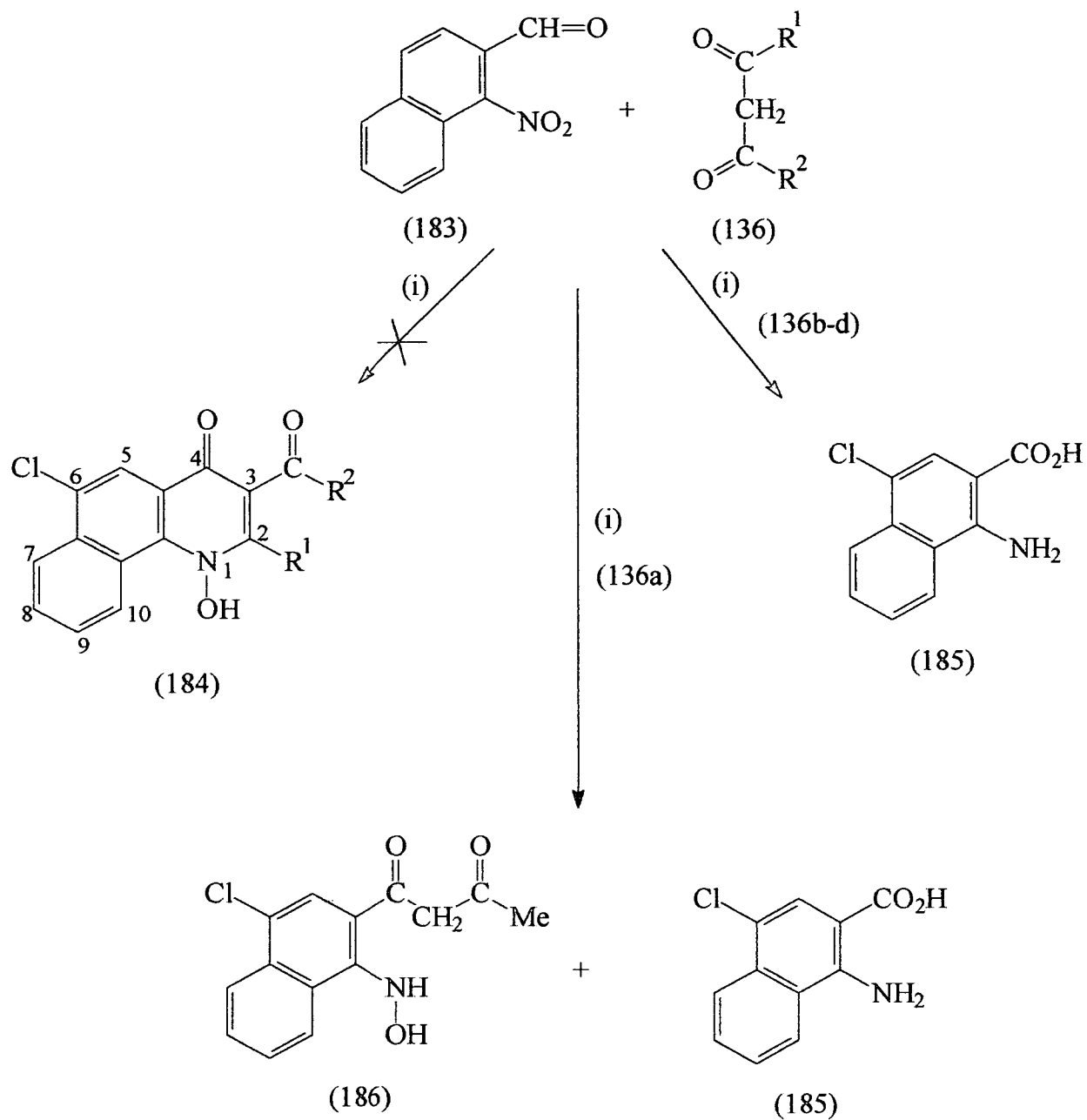


(i) HNO_3 , AcOH , 0°C .

(ii) $\text{Me}_2\text{NCH}(\text{OMe})_2$, DMF, reflux.

(iii) NaIO_4 , THF, room temp.

Scheme 40



	<u>R</u> ¹	<u>R</u> ²
a;	Me	Me
b;	Me	Ph
c;	Ph	Ph
d;	Me	OEt

(i) HCl(g), DME, 0°C.

Scheme 41

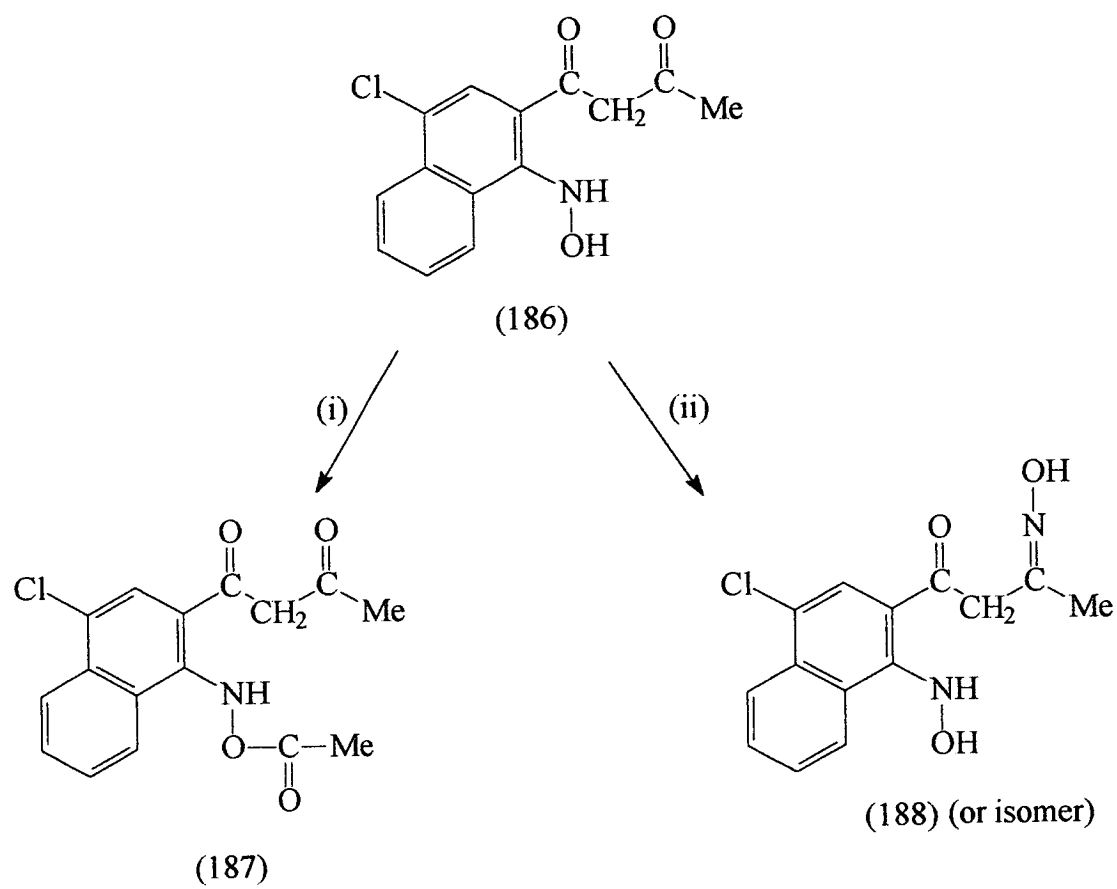
2. STUDIES ON THE SYNTHESIS OF N-HYDROXY BENZOQUINOLINONES BY ACID- CATALYSED CYCLISATION REACTIONS OF ORTHO-SUBSTITUTED NITRONAPHTHALENE DERIVATIVES

2.1 Studies on the Acid- catalysed Cyclisation Reactions of 1-Nitro-2-naphthylidene Derivatives to 1-Hydroxy-4-benzoquinolinones

Initially (Scheme 40) 1-nitro-2-naphthaldehyde (183) was obtained which was required for the synthesis (Scheme 41) of the novel N-hydroxybenzoquinolinones (184). The formation (Scheme 40) of this key starting material was made possible by recent work⁸⁰ describing the synthesis of 2-nitroaldehydes of this type.

2-Methylnaphthalene (180) was nitrated using a known⁸¹ literature method to give 2-methyl-1-nitronaphthalene (181) though only in low yield (39%). Heating 2-methyl-1-nitronaphthalene (181) with N,N-dimethylformamide dimethyl acetal in dimethylformamide under reflux afforded the enamine (182) in this case in high yield (99%) which had a melting point in agreement with the literature value⁸². The enamine derivative (182) was smoothly converted in high yield (95%) into the known⁸² 1-nitro-2-naphthaldehyde (183) by reaction with sodium periodate in aqueous tetrahydrofuran. The nitronaphthaldehyde (183) was identified by its melting point and IR spectrum.

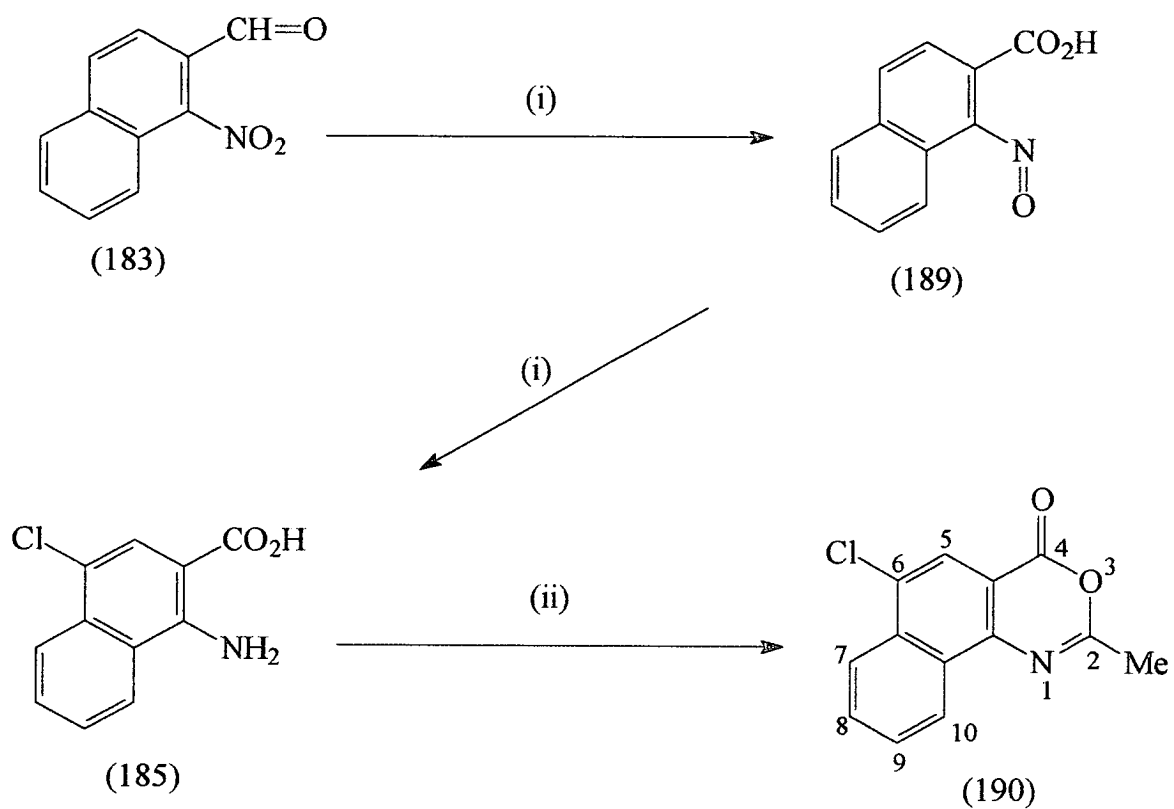
Initially (Scheme 41) the reaction of 1-nitro-2-naphthaldehyde (183) with pentane-2,4-dione (136a) in the presence of hydrogen chloride as catalyst was investigated. This reaction failed to give the corresponding N-hydroxybenzoquinolinone (184a), but instead afforded only a low yield of one identifiable product whose combustion analysis and mass spectrum were consistent with the molecular formula $C_{14}H_{12}ClNO_3$. This formula together with the presence of absorption at 3355, 3215, and 1706 and 1644 cm^{-1} due to NH, OH and carbonyl absorption in the compound's IR spectrum allow its formulation as the hydroxylamine derivative (186). The hydroxylamine derivative (186) also had 1H and ^{13}C NMR spectra in accord with its assigned structure.



(i) AcCl , Et_3N , dioxane, room temp.

(ii) $\text{NH}_2\text{OH} \cdot \text{HCl}$, Na_2CO_3 , EtOH , room temp.

Scheme 42



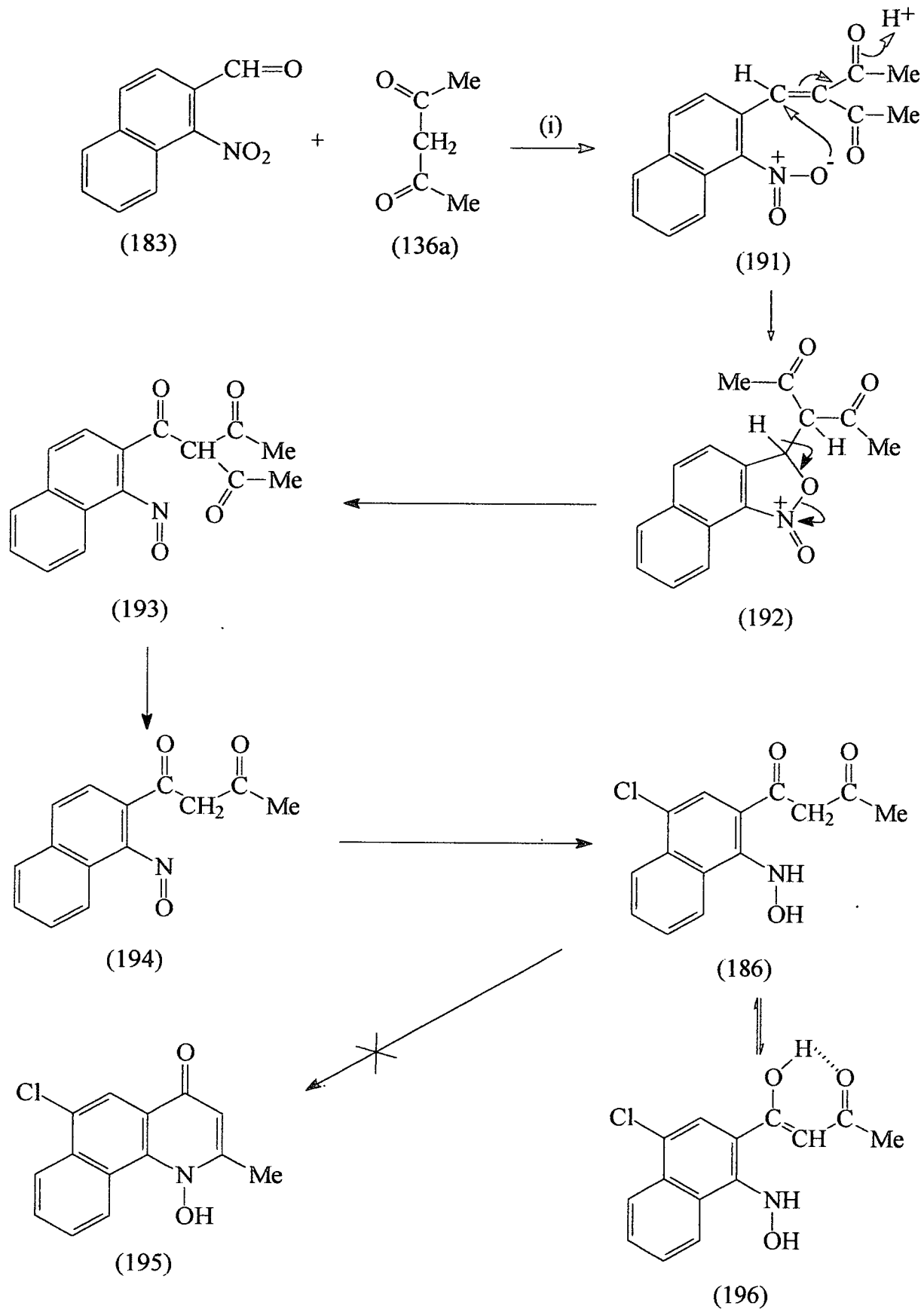
(i) HCl(g) , DME, 0°C .
(ii) Ac_2O , reflux.

Scheme 43

Further evidence (Scheme 42) for the structure of the hydroxylamine derivative (186) was provided by its conversion into an N-acetoxy derivative (187) which was formed by reaction of the hydroxylamine derivative (186) with acetyl chloride in the presence of base. The N-acetoxy derivative (187) gave a combustion analysis and had spectroscopic properties fully consistent with its assigned structure. The 1,3-diketone (186) also afforded a mono oxime derivative (188)(or isomer) whose combustion analysis and mass, IR and ^1H NMR spectra were in good agreement with its structure. It is not known which carbonyl group in the 1,3-diketone (186) has reacted with hydroxylamine and it is possible that an isomer of the structure (188) has been formed. Unfortunately the attempted oxidation of the hydroxylamine derivative (186) using manganese dioxide in dimethoxyethane failed to give the corresponding nitroso compound, instead affording only an intractable solid.

The reaction (Scheme 41) of 1-nitro-2-naphthaldehyde (183) with pentane-2,4-dione (136a) using hydrogen chloride as the catalyst over a longer reaction time also failed to produce the N-hydroxybenzoquinolinone (184a). This reaction afforded two products, one of which was the hydroxylamine derivative (186) and the other was tentatively identified by its mass, IR and ^1H NMR data as the aminonaphthoic acid derivative (185). In practice the attempted reactions of the nitronaphthaldehyde (183) with various 1,3-diacylmethane compounds [1-phenylbutane-1,3-dione (136b), 1,3-diphenylpropane-1,3-dione (136c), or ethyl 3-oxobutanoate (136d)] in the presence of hydrogen chloride also gave the aminonaphthoic acid derivative (185) as the only identifiable product. The aminonaphthoic acid derivative (185) was also formed (Scheme 43) when the nitronaphthaldehyde (183) was exposed to hydrogen chloride in the absence of any other reagent. Evidence (Scheme 43) for the structure of the aminonaphthoic acid derivative (185) was also provided by its conversion into the oxazine derivative (190) in high yield (78%), by heating under reflux in acetic anhydride. The oxazine derivative (190) had analytical and spectroscopic properties fully in agreement with its assigned structure.

The mechanism by which the aminonaphthoic acid derivative (185) is formed from 2-nitronaphthaldehyde (183) in the presence of hydrogen chloride is not entirely clear. However it is possible that by analogy with the known⁸³ conversion of



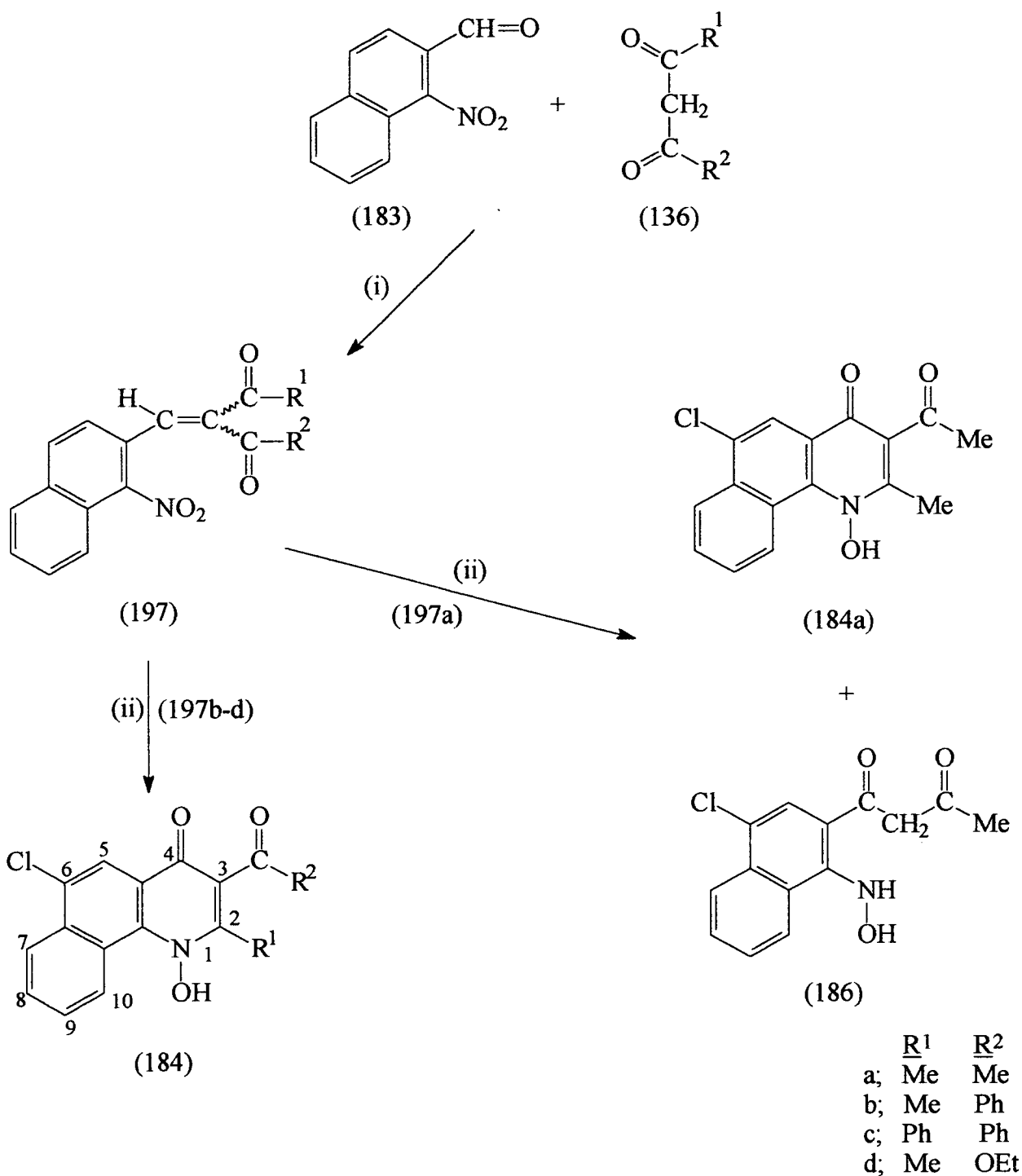
(i) $\text{HCl}_{(g)}$, DME, 0°C .

Scheme 44

2-nitrobenzaldehyde into 2-nitrosobenzoic acid, 2-nitronaphthaldehyde (183) initially affords 2-nitrosobenzoic acid (189). The formation of the aminonaphthoic acid derivative (185) from the latter is then consistent with the reported⁸⁴ formation of 2-amino-5-chlorobenzoic acid from 2-nitrosobenzoic acid in the presence of hydrogen chloride. It may be that the aminonaphthoic acid derivative (185) is formed via a complex reaction involving a disproportionation between two 4-chloro-1-hydroxyaminonaphthalene-2-carboxylic acid molecules. Further work is necessary to evaluate how the aminonaphthoic acid derivative (185) is obtained from the reaction of hydrogen chloride with the nitronaphthaldehyde (183).

Since it was possible that the inefficient condensation (Scheme 41) of the nitronaphthaldehyde (183) with diacylmethane derivatives (136) in the presence of hydrogen chloride was due to the formation of water in the early stages of reaction it was decided to investigate the result of adding molecular sieves to absorb the water formed. However 1-nitro-2-naphthaldehyde (183) reacted with 1-phenylbutane-1,3-dione (136b) in the presence of hydrogen chloride and molecular sieves to afford only a low yield of a single product identified on the basis of its combustion analysis and mass, IR and ¹H NMR spectra as 1-amino-2,4-dichloronaphthalene. The mode of formation of this completely unexpected product is unknown and would require a deep seated transformation of the nitronaphthaldehyde (183) possibly through the intermediacy of the chloroaminonaphthoic acid (185) as discussed before.

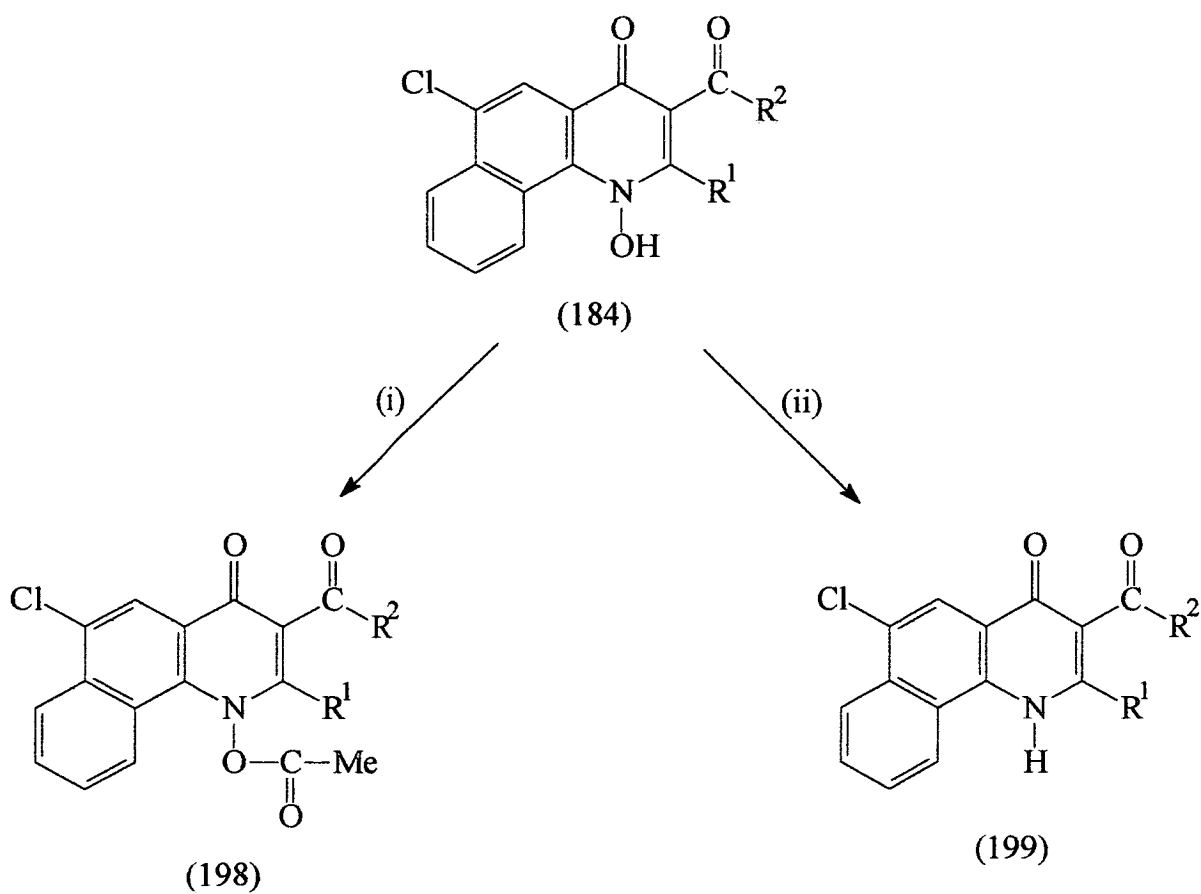
The mechanism (Scheme 44) of the reaction of 1-nitro-2-naphthaldehyde (183) with pentane-2,4-dione (136a) can be explained by the initial condensation of the two components to give the 1-nitronaphthylidene (191). By analogy with related processes discussed before (see Chapter 1, Section 3.2, page 18 and Scheme 20) nucleophilic attack [(191)→(192)→(193)] by the nitro group in the naphthylidene derivative (191) on the naphthylidene side chain then affords the nitroso- ketone intermediate (193). Deacylation of the latter to give the diketone derivative (194) followed by indirect reduction by hydrogen chloride would then give the chlorinated hydroxyaminonaphthalene (186) isolated as product. The ¹H NMR spectrum of diketone derivative (186) shows signals assignable to exchangeable protons of a methylene group. This indicates that the diketone (186) exists at least partly in



(i) piperidine, solvent, room temp. or 50°C.

(ii) $\text{HCl}_{(g)}$, DME, 0°C.

Scheme 45



	<u>R¹</u>	<u>R²</u>
a;	Me	Me
b;	Me	Ph
c;	Ph	Ph
d;	Me	OEt

- (i) AcCl, Et₃N, dioxane, room temp.
 (ii) Na₂S₂O₄, EtOH, H₂O, reflux.

Scheme 46

solution as the enol tautomer (196)(or the alternative isomer). Since hydrogen bonding in the enol tautomer (196) locks the acetyl group in a position away from the hydroxylamine group, this effect may explain why the hydroxylamine derivative (186) fails to undergo cyclisation to the N-hydroxybenzoquinolinone (195).

It is possible that the inefficiency of the condensation (Scheme 41) of the nitronaphthaldehyde (181) with diacylmethane derivatives (136) in the presence of hydrogen chloride to give the corresponding chlorinated N-hydroxybenzoquinolinones (184) is due to the inefficient initial formation (Scheme 45) of the nitronaphthylidene derivatives (197) which are plausible intermediates in such cyclisations (see Chapter 1, Section 3.2, page 18 and Scheme 20). It was therefore decided to preform such nitronaphthylidene derivatives (197) in order to investigate their possible hydrogen chloride catalysed cyclisation to the corresponding N-hydroxybenzoquinolinone derivatives (184). In practice 1-nitro-2-naphthaldehyde (183) underwent piperidine catalysed condensation with pentane-2,4-dione (136a) in glacial acetic acid to give a low yield (28%) of a product whose combustion analysis and spectroscopic properties showed it to be the required nitronaphthylidene derivative (197a). Extending the reaction time or changing the solvent to ethanol or dimethoxyethane resulted only in a marginal improvement in the yield of the nitronaphthylidene derivative (197a) to ca 45%, with large amounts of unreacted nitronaphthaldehyde (183) also being recovered. However by increasing the amounts of pentane-2,4-dione (136a) and piperidine catalyst used in the reaction with the nitronaphthaldehyde (183) the yield of the nitronaphthylidene derivative (197a) was raised to 74%.

Attention was next turned to investigating the behaviour of the nitronaphthylidene derivative (197a) towards hydrogen chloride. Treatment with hydrogen chloride in dimethoxyethane converted the nitronaphthylidene derivative (197a) into a separable mixture of the hydroxylamine derivative (186) (20%) and a product (58%) which gave analytical and spectroscopic data consistent with its formulation as the N-hydroxybenzoquinolinone derivative (184a). Further characterisation (Scheme 46) of the N-hydroxybenzoquinolinone (184a) was achieved by its conversion into the N-acetoxybenzoquinolinone derivative (198a). Treatment of the

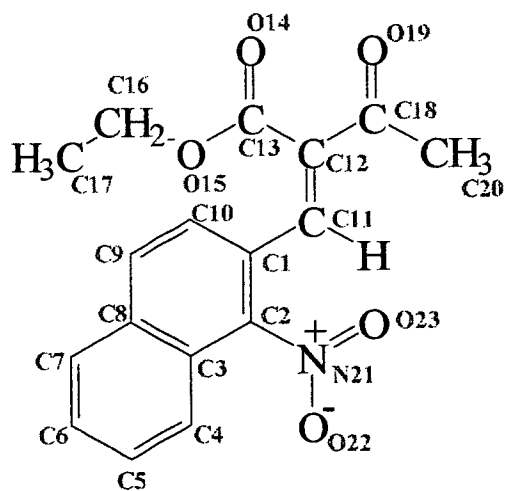
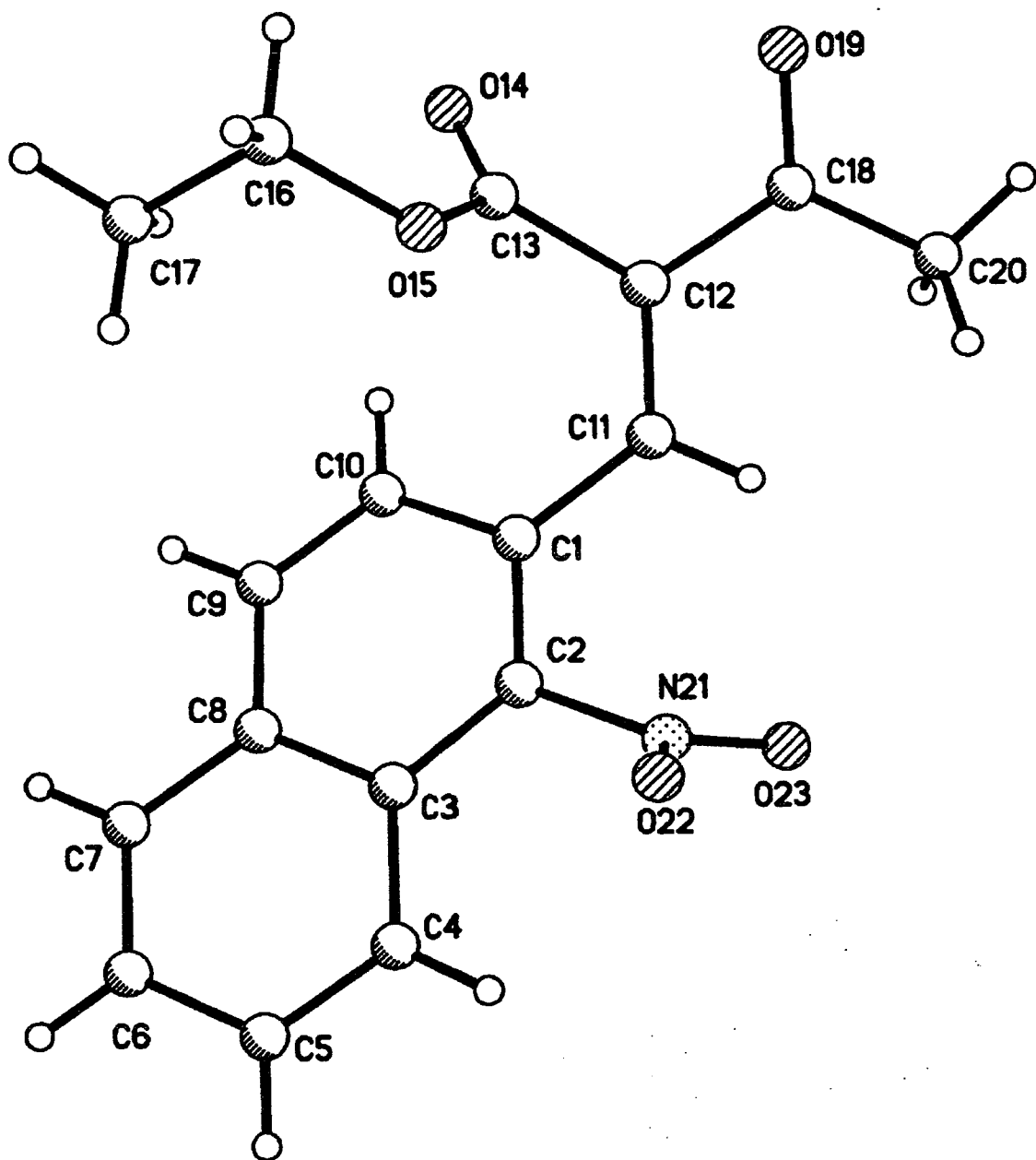
N-hydroxybenzoquinolinone (184a) with acetyl chloride in the presence of triethylamine afforded a good yield of a product which showed characteristic IR absorption at 1800 cm^{-1} due to an N-acetoxy group together with combustion analysis and mass and ^1H NMR spectra consistent with its N-acetoxy benzoquinolinone structure (198a). The N-hydroxybenzoquinolinone (184a) was also reduced to the parent benzoquinolinone (199a) in high yield, by heating under reflux with sodium dithionite in aqueous ethanol. It was found that the reaction of the nitronaphthylidene derivative (197a) with hydrogen chloride over a shorter reaction time gave an increased yield (77%) of the N-hydroxybenzoquinolinone (184a) together with a low yield (20%) of the hydroxylamine derivative (186).

Extension of the strategy outlined in Scheme 45 was investigated as a general route to otherwise inaccessible N-hydroxybenzoquinolinone derivatives. The condensation reactions of 1-nitro-2-naphthaldehyde (183) with 1-phenylbutane-1,3-dione (136b), 1,3-diphenylpropane-1,3-dione (136c), and ethyl 3-oxobutanoate (136d) were investigated in the anticipation of obtaining the nitronaphthylidene derivatives (194b-d), which it was hoped would undergo acid-catalysed cyclisation to give the corresponding N-hydroxybenzoquinolinones (184b-d). In practice 1-nitro-2-naphthaldehyde (183) reacted with 1-phenylbutane-1,3-dione (136b) in glacial acetic acid in the presence of piperidine to afford a moderate yield of the corresponding nitronaphthylidene derivative (197b) which had analytical and spectroscopic properties consistent with its structure. Further work was carried out in an attempt to find improved conditions for this condensation reaction. Extending the reaction time of the reaction of 1-nitro-2-naphthaldehyde (183) with 1-phenylbutane-1,3-dione (136b) in the presence of piperidine gave the nitronaphthylidene derivative (197b) in high yield. In contrast repeating the condensation reaction at elevated temperature gave only the nitronaphthylidene derivative (197b) in poor yield. Similarly no improvement in the condensation of 1-nitro-2-naphthaldehyde (183) and the active diacylmethane derivative (136b) resulted when the reaction was carried out in dimethylformamide. Changing the solvent to dimethoxyethane in the reaction of 1-nitro-2-naphthaldehyde (183) with 1-phenylbutane-1,3-dione (136b) using piperidine as the catalyst gave the nitronaphthylidene derivative (197b) in low yield (25%).

The reaction of the nitronaphthylidene derivative (197b) with hydrogen chloride gave the corresponding N-hydroxybenzoquinolinone (184b) in high yield (88%). The N-hydroxybenzoquinolinone (184b) analysed correctly and gave mass, IR and ^1H NMR spectra consistent with its assigned structure. It also reacted (Scheme 46) with acetyl chloride in the presence of triethylamine to afford the N-acetoxy derivative (198b) which showed characteristic⁷² IR absorption at 1806 cm^{-1} . The N-hydroxybenzoquinolinone (184b) also underwent orthodox reduction using sodium dithionite in aqueous ethanol to afford the reduced benzoquinolinone (199b) in good yield (92%). It was found that the reaction time of the nitronaphthylidene derivative (197b) with hydrogen chloride could be shortened without any substantial decrease in the yield of the N-hydroxybenzoquinolinone derivative (184b).

Attention (Scheme 45) was next turned to the condensation of 1-nitro-2-naphthaldehyde (183) with 1,3-diphenylpropane-1,3-dione (136c) to form the nitronaphthylidene derivative (197c). However 1-nitro-2-naphthaldehyde (183) failed to react with 1,3-diphenylpropane-1,3-dione (136c) in glacial acetic acid in the presence of piperidine under standard conditions, with the starting materials being recovered unchanged as demonstrated by TLC. Extending the time of this reaction however gave the expected nitronaphthylidene derivative (197c) though in low yield (17%). In contrast carrying out the condensation reaction of the nitronaphthaldehyde (183) with the diacylmethane derivative (136c) at elevated temperature resulted in the formation of the naphthylidene derivative (197c) in low yield (18%). Other methods were investigated of condensing 1-nitro-2-naphthaldehyde (183) with the diacylmethane derivative (136c) efficiently to give the nitronaphthylidene derivative (197c). However the reaction of 1-nitro-2-naphthaldehyde (183) with 1,3-diphenylpropane-1,3-dione (136c) using a catalytic amount of piperidine in dimethoxyethane gave the nitronaphthylidene derivative (197c) in poor yield (3%). Extending the time of this reaction gave no improvement in the yield of the nitronaphthylidene derivative (197c).

Investigations were also carried out on the piperidine catalysed condensation reaction of ethyl 3-oxobutanoate (136d) with 1-nitro-2-naphthaldehyde (183) in glacial acetic



(197d)

Figure 8

Table 1. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for the Z alkene (197d). U(eq) is defined as one third of the trace of the orthogonalised U_{ij} tensor.

	x	y	z	U(eq)
C(1)	8347(2)	932(2)	754(2)	36(1)
C(2)	9435(2)	1442(2)	789(2)	34(1)
C(3)	10535(2)	939(2)	1356(2)	35(1)
C(4)	11662(2)	1452(2)	1366(2)	39(1)
C(5)	12677(2)	901(2)	1938(2)	47(1)
C(6)	12640(2)	-156(3)	2539(2)	50(1)
C(7)	11584(2)	-672(2)	2539(2)	45(1)
C(8)	10509(2)	-152(2)	1931(2)	38(1)
C(9)	9394(2)	-697(2)	1879(2)	41(1)
C(10)	8359(2)	-182(2)	1302(2)	41(1)
C(11)	7228(2)	1514(2)	183(2)	38(1)
C(12)	6237(2)	1536(2)	586(2)	37(1)
C(13)	6137(2)	955(2)	1699(2)	39(1)
O(14)	5494(2)	131(2)	1728(2)	54(1)
O(15)	6824(2)	1477(2)	2628(2)	46(1)
C(16)	6776(2)	990(3)	3764(2)	59(1)
C(17)	7559(2)	-65(3)	4084(3)	63(1)
C(18)	5151(2)	2192(2)	-34(2)	42(1)
O(19)	4370(2)	2362(2)	472(2)	62(1)
C(20)	5064(2)	2657(3)	-1231(2)	50(1)
N(21)	9460(2)	2631(2)	274(2)	38(1)
O(22)	9882(2)	3434(2)	931(2)	60(1)
O(23)	9072(2)	2758(2)	-767(2)	63(1)

Table 2. Bond lengths [Å] and angles [deg] for the *Z* alkene (197d).

C(1)-C(2)	1.381(3)
C(1)-C(10)	1.416(3)
C(1)-C(11)	1.467(3)
C(2)-C(3)	1.411(3)
C(2)-N(21)	1.480(3)
C(3)-C(8)	1.413(3)
C(3)-C(4)	1.429(3)
C(4)-C(5)	1.359(4)
C(5)-C(6)	1.397(4)
C(6)-C(7)	1.359(4)
C(7)-C(8)	1.409(3)
C(8)-C(9)	1.423(3)
C(9)-C(10)	1.360(3)
C(11)-C(12)	1.349(3)
C(12)-C(18)	1.494(3)
C(12)-C(13)	1.502(3)
C(13)-C(14)	1.200(3)
C(13)-C(15)	1.329(3)
C(15)-C(16)	1.466(3)
C(16)-C(17)	1.493(4)
C(18)-O(19)	1.217(3)
C(18)-C(20)	1.491(3)
N(21)-O(23)	1.213(3)
N(21)-O(22)	1.218(3)
C(2)-C(1)-C(10)	116.8(2)
C(2)-C(1)-C(11)	121.9(2)
C(10)-C(1)-C(11)	121.3(2)
C(1)-C(2)-C(3)	124.2(2)
C(1)-C(2)-N(21)	118.5(2)
C(3)-C(2)-N(21)	117.10(19)
C(2)-C(3)-C(8)	117.2(2)
C(2)-C(3)-C(4)	124.2(2)
C(8)-C(3)-C(4)	118.5(2)
C(5)-C(4)-C(3)	120.0(2)
C(4)-C(5)-C(6)	121.0(2)
C(7)-C(6)-C(5)	120.5(2)
C(6)-C(7)-C(8)	120.6(2)
C(7)-C(8)-C(3)	119.3(2)
C(7)-C(8)-C(9)	121.8(2)
C(3)-C(8)-C(9)	118.9(2)
C(10)-C(9)-C(8)	121.4(2)
C(9)-C(10)-C(1)	121.3(2)
C(12)-C(11)-C(1)	125.6(2)
C(11)-C(12)-C(18)	121.9(2)
C(11)-C(12)-C(13)	123.8(2)
C(18)-C(12)-C(13)	114.29(19)
O(14)-C(13)-O(15)	125.1(2)
O(14)-C(13)-C(12)	123.1(2)
O(15)-C(13)-C(12)	111.8(2)
C(13)-O(15)-C(16)	116.2(2)
O(15)-C(16)-C(17)	112.1(2)
O(19)-C(18)-C(20)	121.7(2)

Table 2. (cont.) Bond lengths [Å] and angles [deg] for the *cis* alkene (197d).

O(19)-C(18)-C(12)	8.7(2)
C(20)-C(18)-C(12)	119.6(2)
O(23)-N(21)-O(22)	123.5(2)
O(23)-N(21)-C(2)	119.1(2)
O(22)-N(21)-C(2)	117.42(19)

Table 3. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for the Z alkene (197d).

The anisotropic displacement factor exponent takes the form: $-2 \pi^2 [h^2 a^{*2} U_{11} + \dots + 2 h k a^* b^* U_{12}]$.

	U11	U22	U33	U23	U13	U12
C(1)	36(1)	39(1)	36(1)	-1(1)	18(1)	0(1)
C(2)	38(1)	36(1)	33(1)	-1(1)	18(1)	0(1)
C(3)	36(1)	39(1)	34(1)	-5(1)	17(1)	-1(1)
C(4)	36(1)	45(1)	41(1)	-2(1)	17(1)	-3(1)
C(5)	36(1)	57(2)	48(2)	-5(1)	15(1)	-1(1)
C(6)	42(1)	58(2)	51(2)	-1(1)	10(1)	10(1)
C(7)	48(2)	43(1)	46(2)	1(1)	15(1)	6(1)
C(8)	41(1)	39(1)	38(1)	-1(1)	19(1)	5(1)
C(9)	45(1)	38(1)	48(1)	3(1)	24(1)	1(1)
C(10)	39(1)	41(1)	50(1)	-1(1)	23(1)	-3(1)
C(11)	37(1)	42(1)	41(1)	0(1)	17(1)	-3(1)
C(12)	37(1)	38(1)	39(1)	-2(1)	15(1)	-2(1)
C(13)	34(1)	43(1)	44(1)	2(1)	20(1)	5(1)
O(14)	48(1)	59(1)	58(1)	9(1)	21(1)	-10(1)
O(15)	54(1)	49(1)	39(1)	-1(1)	20(1)	-1(1)
C(16)	75(2)	67(2)	41(2)	-1(1)	28(1)	2(2)
C(17)	66(2)	73(2)	51(2)	17(2)	17(1)	2(2)
C(18)	39(1)	46(1)	45(1)	2(1)	17(1)	2(1)
O(19)	49(1)	82(2)	67(1)	18(1)	35(1)	21(1)
C(20)	47(1)	61(2)	45(2)	11(1)	15(1)	8(1)
N(21)	33(1)	41(1)	41(1)	2(1)	15(1)	0(1)
O(22)	76(1)	42(1)	61(1)	-5(1)	11(1)	-9(1)
O(23)	85(2)	56(1)	45(1)	10(1)	13(1)	-7(1)

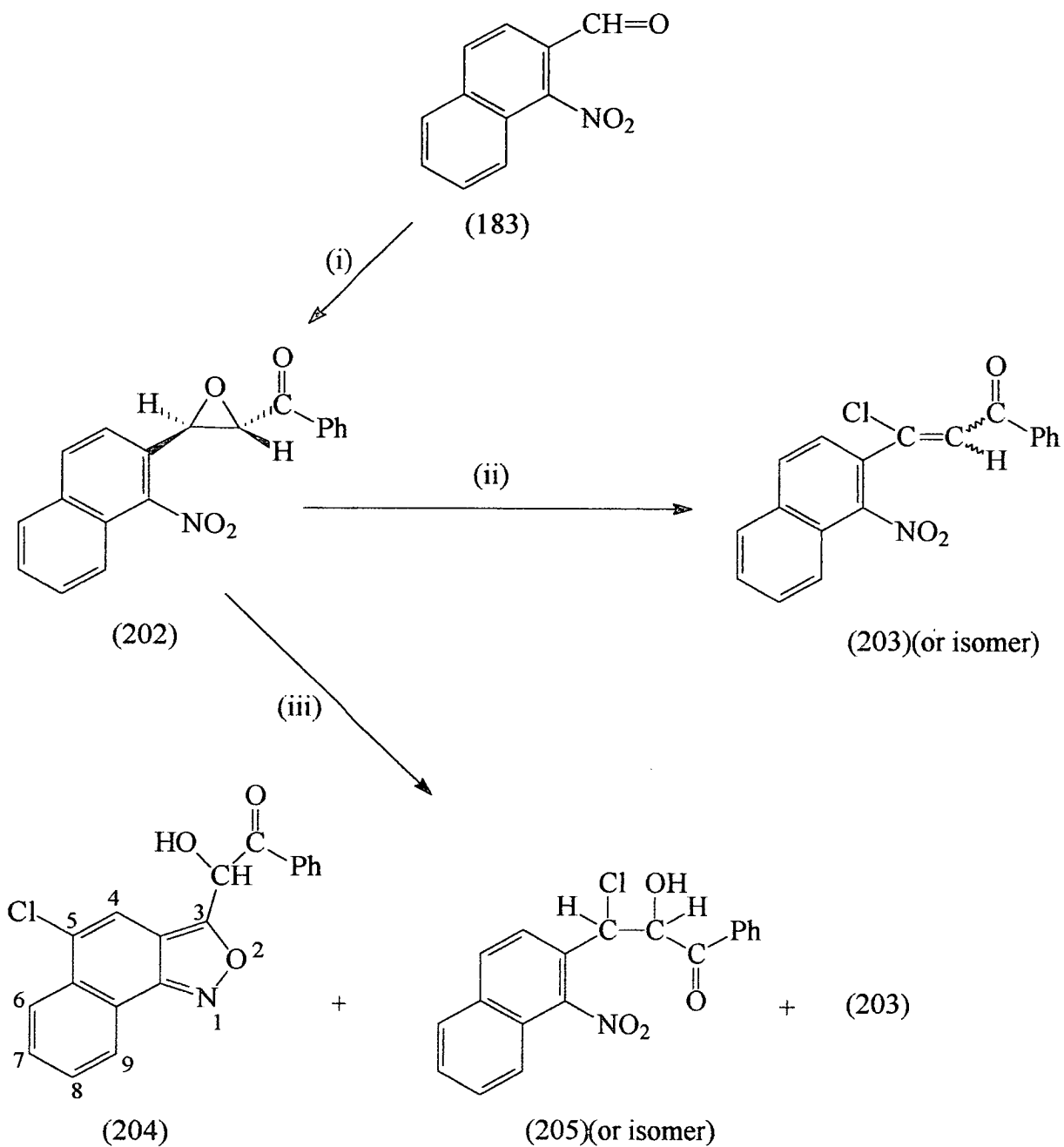
Table 4. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for the *Z* alkene (197d).

	x	y	z	U(eq)
H(4)	11702	2177	973	47
H(5)	13423	1240	1929	56
H(6)	13358	-516	2950	60
H(7)	11570	-1391	2952	54
H(9)	9371	-1435	2255	50
H(10)	7629	-578	1267	49
H(11)	7198	1909	-532	46
H(16A)	5948	764	3743	70
H(16B)	7022	1606	4368	70
H(17A)	7501	-362	4846	94
H(17B)	8383	159	4120	94
H(17C)	7309	-683	3495	94
H(20A)	4302	3061	-1512	75
H(20B)	5120	1999	-1754	75
H(20C)	5713	3215	-1213	75

acid. This reaction afforded a low yield of an inseparable mixture of the *E* and *Z* isomers of the nitronaphthylidene (197d) which analysed correctly and had mass, IR and ¹H NMR spectra consistent with the proposed isomer mixture together with the *Z* nitronaphthylidene derivative (197d) also in low yield whose structure was confirmed by X-ray analysis (see Figure 8, Tables 1-4).

Since the piperidine catalysed condensation of the nitronaphthaldehyde (183) and ethyl 3-oxobutanoate (136d) was inefficient, investigations were carried out to find improved reaction conditions for this reaction. The condensation of 1-nitro-2-naphthaldehyde (183) with ethyl 3-oxobutanoate (136d) using a catalytic amount of piperidine afforded a mixture of the *E* and *Z* isomers of the nitronaphthylidene derivative (197d) in good yield. Extending the time of this reaction gave the mixture of the *E* and *Z* isomers of the nitronaphthylidene derivative (197d) in similar yield. In contrast the mixture of the *E* and *Z* isomers of the nitronaphthylidene derivative (197d) was isolated in high yield when the condensation reaction was carried out in the presence of excess ethyl 3-oxobutanoate (136d).

The reaction (Scheme 45) of the *Z* nitronaphthylidene derivative (197d) with hydrogen chloride afforded a good yield (68%) of the expected N-hydroxybenzoquinolinone (184d) whose structure was verified by its analytical and spectroscopic properties and its conversion in high yield under standard conditions (see before) into the N-acetoxy derivative (198d) and the parent reduced benzoquinolinone (199d). The unresolved *E/Z* isomeric mixture of the nitronaphthylidene derivative (197d) also cyclised in the presence of hydrogen chloride to the N-hydroxybenzoquinolinone (184d) in good yield (76%). Somewhat surprisingly shortening the time of this reaction resulted in a substantially increased yield (98%) of the N-hydroxybenzoquinolinone derivative (184d). The N-hydroxybenzoquinolinones (184a-d) are formed by a similar mechanism as shown in Scheme 44. Once again nucleophilic attack by the nitro group of the nitronaphthylidene derivative (191) on the adjacent naphthylidene side-chain results in the formation [(191)→(192)→(193)] of the nitroso naphthalene derivative (193). The indirect reduction of the nitroso derivative (193) by its reaction with hydrogen chloride (see Chapter 1, Section 3.2, page 18 and Scheme 20) followed by



(i) PhCOCH_2Br , NaOMe, MeOH, room temp.

(ii) $\text{HCl}_{(g)}$, dioxane, 11°C .

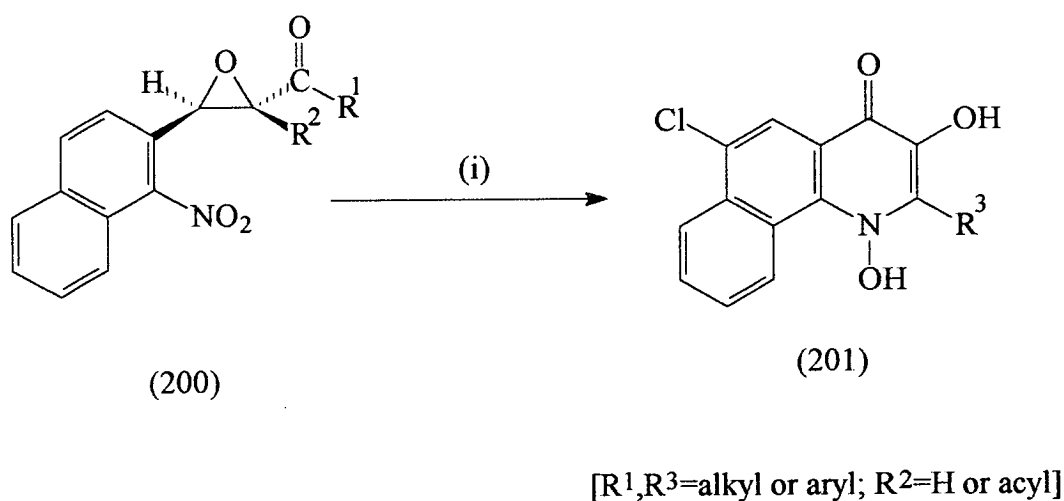
(iii) $\text{HCl}_{(g)}$, DME, 0°C .

Scheme 48

cyclisation of the resulting hydroxylamine intermediate accounts for the formation of the benzoquinolinone derivative (184a).

2.2 Studies on the Acid- catalysed Cyclisation Reactions of 1-Nitronaphth-2-yloxirane Derivatives to 1,3-Dihydroxy-4-benzoquinolinones

Studies carried out in parallel with the investigation of the acid- catalysed formation of N-hydroxybenzoquinolinones from 2-nitronaphthyl derivatives involved the hydrogen chloride catalysed transformation (Scheme 47) of 2-nitronaphthyloxirane derivatives (200) into novel 1,3-dihydroxybenzoquinolinones (201). The initial strategy (Scheme 48) for these transformations involved the formation of the *trans* nitronaphthyloxirane derivative (202) from 1-nitro-2-naphthaldehyde (183) and the investigation of its behaviour towards hydrogen chloride which it was anticipated would afford the chlorinated 1,3-dihydroxybenzoquinolinone derivative (201; $R^3=Ph$).



(i) Acid.

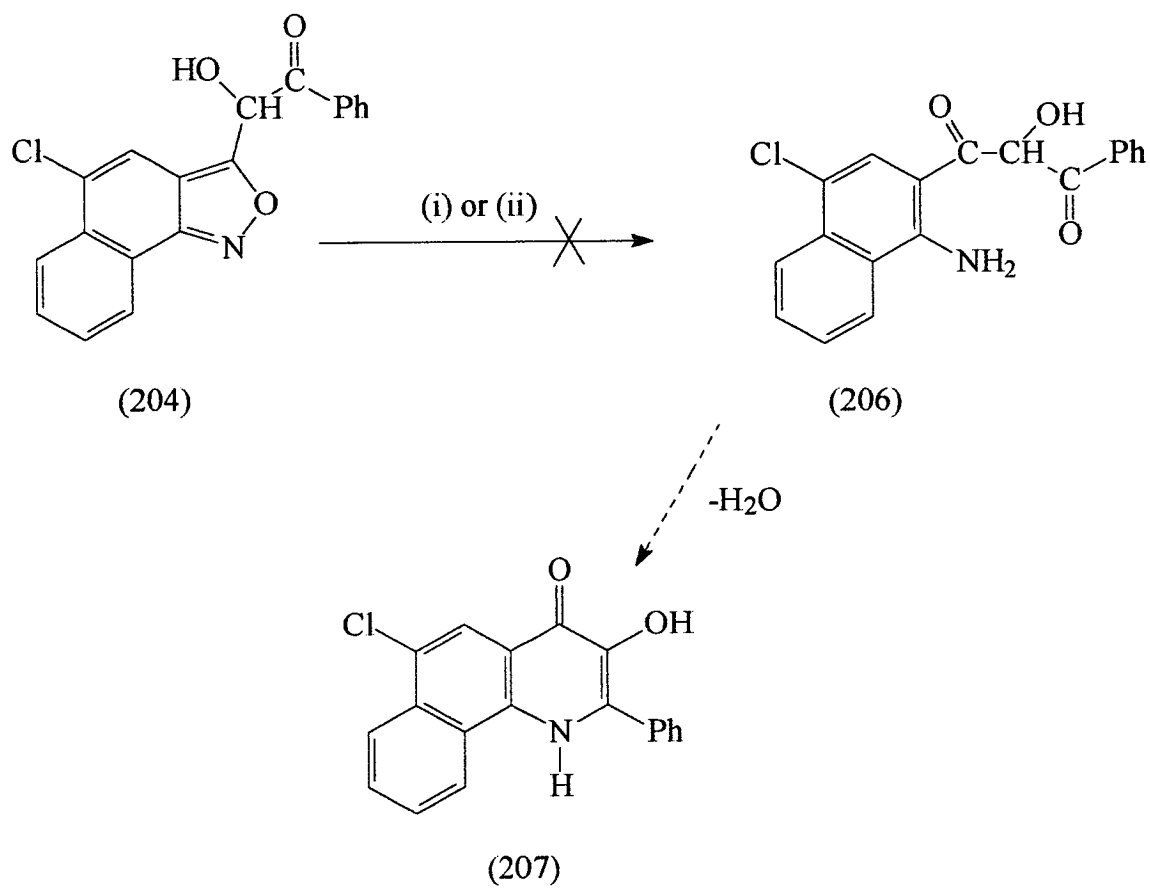
Scheme 47

In practice (Scheme 48) 1-nitro-2-naphthaldehyde (183) reacted smoothly with 2-bromoacetophenone in the presence of methanolic sodium methoxide to afford a product in good yield (89%) with analytical and spectroscopic properties consistent with the *trans* nitronaphthyloxirane derivative (202). The *trans* nitronaphthyloxirane

derivative (202) reacted with hydrogen chloride in dioxane to give a low yield of a product which had combustion analysis and parent ions at m/z 339 and 337 in its mass spectrum consistent with the molecular formula $C_{19}H_{12}ClNO_3$. This molecular formula together with the presence of carbonyl absorption at 1657 cm^{-1} and absorption due to a nitro group at 1526 and 1373 cm^{-1} in its IR spectrum allow the formulation of the product as the chloronitronaphthylidene derivative (203). Furthermore the ^1H NMR spectrum of this product lacked signals due to exchangeable protons. This evidence together with the presence of absorption due to a nitro group in its IR spectrum exclude the alternative isomeric dihydroxybenzoquinolinone structure (201; $R^3=\text{Ph}$) for the product. Unfortunately the ^{13}C NMR spectrum of the chloronaphthylidene derivative (203) was complex and yielded no useful information. An isomeric structure for the chloronitronaphthylidene derivative with the chlorine atom alpha to the benzoyl group cannot be excluded. However the assigned structure (203) is considered more likely on the basis of its formation by dehydration of the corresponding chlorohydrin intermediate (205)(see later).

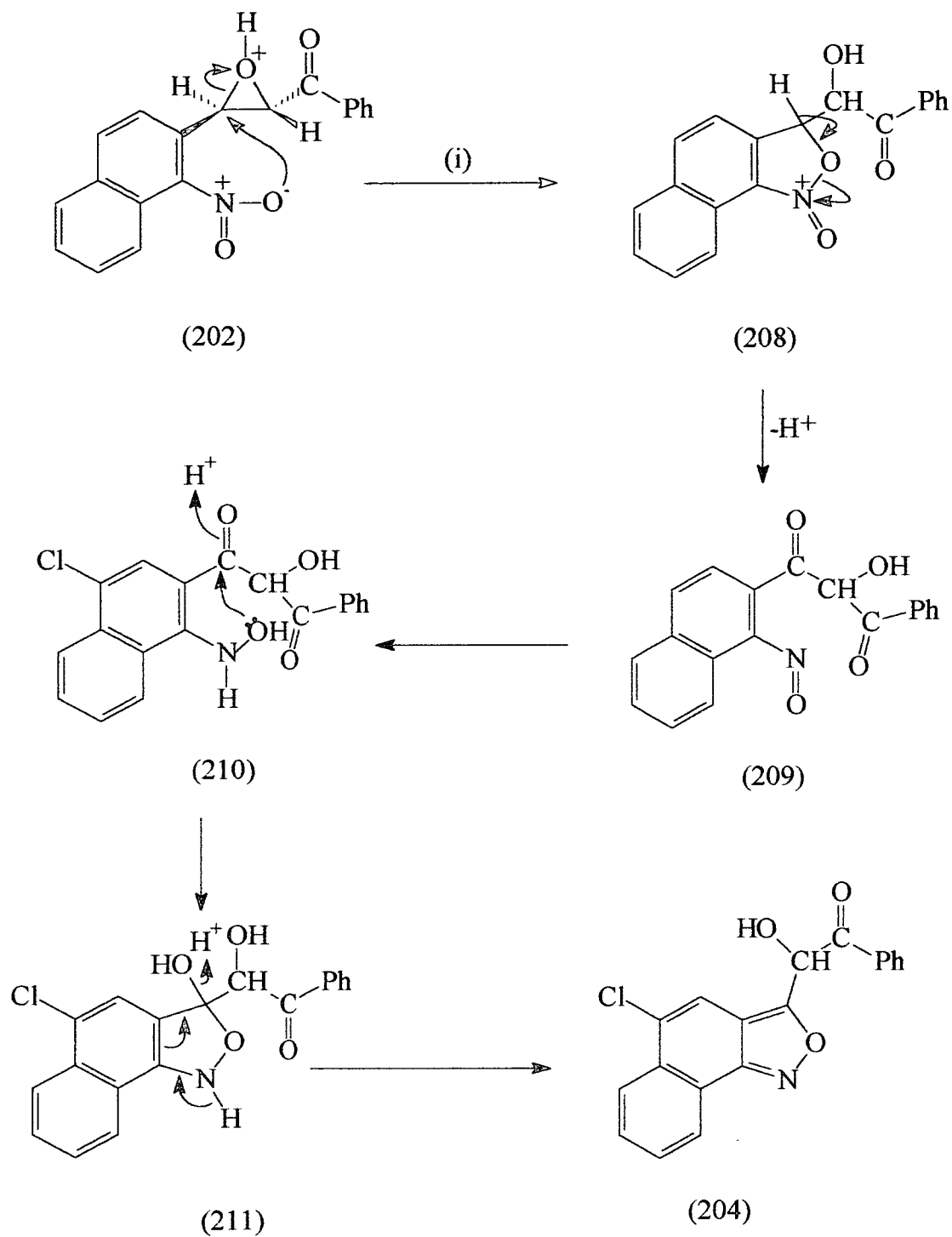
Attempts were also made to characterise the chloronitronaphthylidene derivative (203) by chemical methods. However the attempted reduction of the compound (203) using hydrogen in the presence of palladium-on-charcoal failed to give any identifiable product. The attempted oxidative degradation of the chloronitronaphthylidene derivative (203) was equally uninformative, treatment with chromium trioxide in glacial acetic acid at 100°C affording benzoic acid as the only identifiable product. Conversely the attempted oxidation of the chloronitronaphthylidene derivative (203) with manganese dioxide resulted only in a good recovery (76%) of the unreacted starting material.

It was found (Scheme 48) that the *trans* nitronaphthyloxirane derivative (202) reacted with hydrogen chloride in the alternative solvent dimethoxyethane to afford a low yield (28%) of the chloro naphthylidene derivative (203) as the only identifiable product. However when this reaction was repeated over a longer time three products were isolated, none of which were the hoped for N-hydroxybenzoquinolinone (201; $R^3=\text{Ph}$). The main product (yield 30%) from this reaction was the



- (i) $Na_2S_2O_4$, EtOH, H_2O , reflux.
(ii) H_2 , Pd-C, EtOH, atmos. press.

Scheme 49



(i) $HCl_{(g)}$, DME, $0^\circ C$.

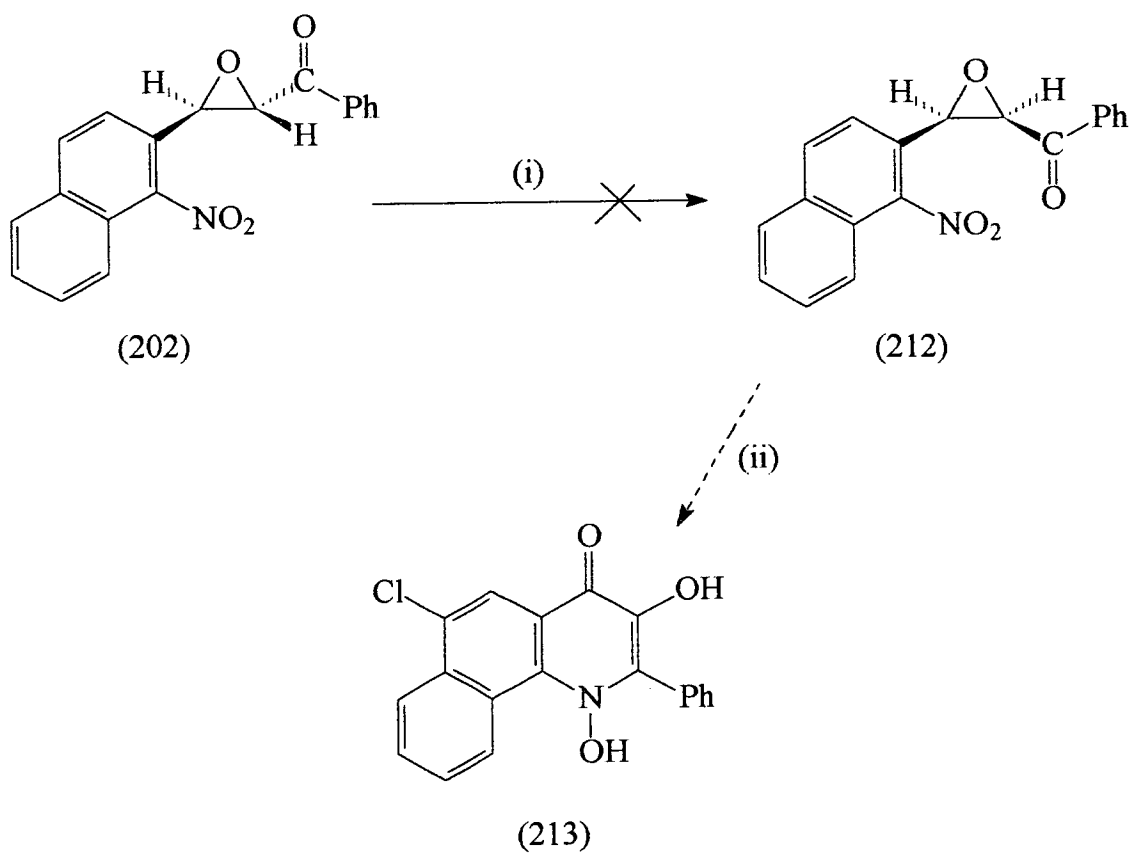
Scheme 50

chloronitronaphthylidene derivative (203). The second product (yield 6%) had mass, IR and ^1H NMR spectra consistent with the chlorohydrin structure (205). The chlorohydrin derivative (205) is presumably the precursor of the chloronitronaphthylidene derivative (203). The formation of the chlorohydrin (205) in the reaction of the nitronaphthyloxirane (202) with hydrogen chloride is an example of a well known⁷⁴ ring-opening reaction of oxirane derivatives in general. The assignment of the structure (205) to the chlorohydrin product rather than the alternative structure with the chlorine atom alpha to the benzoyl group is based on the assumption that initial acid-catalysed opening of the oxirane ring will lead to the more stable naphthylmethyl cation. However further studies are needed to firmly establish the structure (205) for the chlorohydrin product.

The third product (yield 12%) isolated in the reaction of the nitronaphthyloxirane derivative with hydrogen chloride gave a combustion analysis and mass spectrum consistent with the formula $\text{C}_{19}\text{H}_{12}\text{ClNO}_3$. This molecular formula together with the presence of absorption at 3457 cm^{-1} (hydroxy group) as well as carbonyl absorption at 1685 cm^{-1} and the lack of absorption of a nitro group in its IR spectrum allow the formulation of the product as the naphthisoxazole derivative (204). The ^1H and ^{13}C NMR spectra of the product also agree with the assigned naphthisoxazole structure (204).

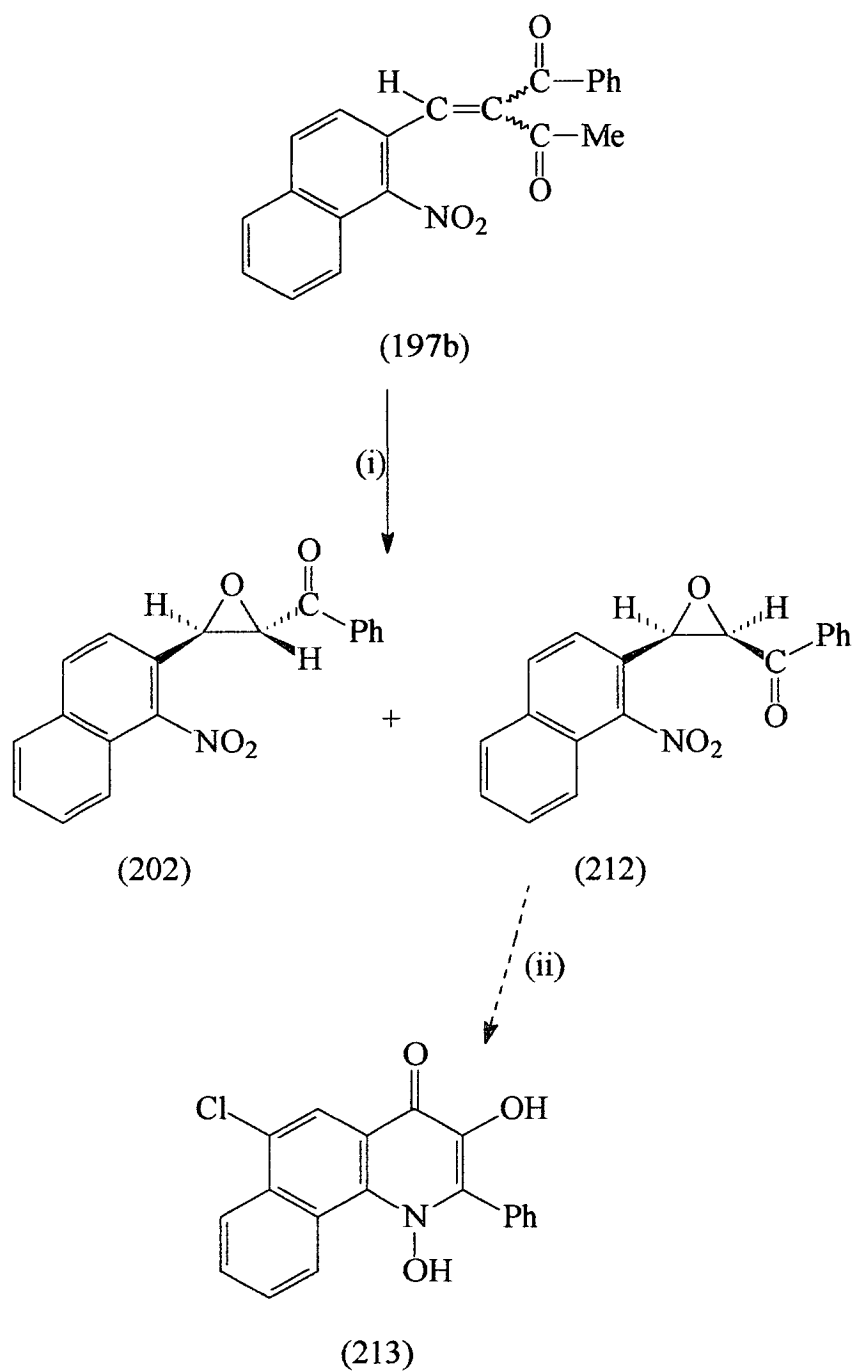
With a view (Scheme 49) to firmly establishing the structure of the isoxazole derivative (204) attempts were made to reduce the compound through N-O bond cleavage to give the amine (206) which it was anticipated might undergo spontaneous cyclisation to the benzoquinolinone derivative (207). However heating the naphthisoxazole derivative (204) under reflux with sodium dithionite in aqueous ethanol afforded only a good recovery of unreacted starting material. Similarly the attempted hydrogenation of the naphthisoxazole derivative (204) in the presence of palladium-on-charcoal also failed to give any identifiable material only an intractable red-brown oil being isolated from this reaction.

A possible mechanism (Scheme 50) for the formation of the naphthisoxazole derivative (204) would involve nucleophilic attack by the nitro group in the



(i) NaOMe, MeOH, room temp.
(ii) HCl(g) , dioxane, 11°C .

Scheme 51



- (i) NaOCl (aqu.), dioxane, room temp.
 (ii) $\text{HCl}_{(\text{g})}$, DME, 0°C .

Scheme 52

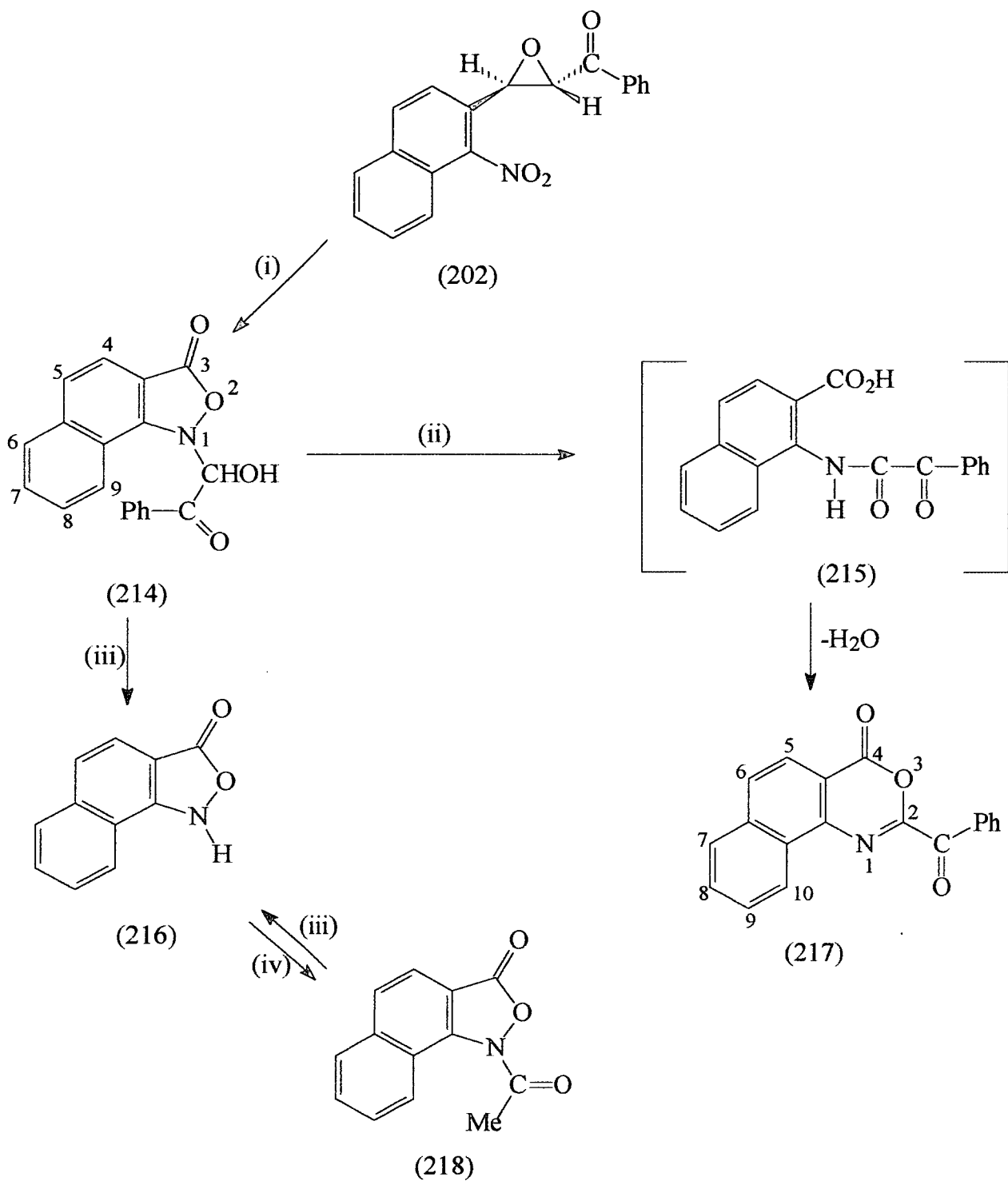
nitronaphthyloxirane derivative (202) on the electrophilic side chain [(202)→(208)→(209)] to afford the nitroso intermediate (209). The latter could then react with hydrogen chloride to give the chlorinated hydroxyamino intermediate (210) subsequent acid- catalysed cyclisation of which [(210)→(211)→(204)] would produce the naphthisoxazole derivative (204).

It is known^{68,69} that *cis* acyl nitrophenyloxirane derivatives are more efficient than the corresponding *trans* oxirane derivatives in undergoing acid- catalysed cyclisation reactions to give the corresponding 1,3-dihydroxyquinolinones. However (Scheme 51) the study of the hydrogen chloride catalysed cyclisation of *cis* acyl nitronaphthyloxirane derivatives was prevented by the failure of attempts to obtain these starting materials. Thus the attempted epimerisation of the *trans* benzoylnitronaphthyloxirane (202) in the presence of methanolic sodium methoxide, unlike the corresponding benzene derivative⁷³, failed to afford the *cis* isomer (212).

Investigations described earlier (see Chapter 2, section 3, page 40 and Scheme 34) demonstrated that diacyl 2-nitrobenzylidene derivatives react with aqueous sodium hypochlorite to afford a separable mixture of the *cis* and *trans* mono acyl 2-nitrophenyloxirane derivatives. The *cis* acyloxirane derivatives were thus made available for acid- catalysed cyclisation to the corresponding chlorinated 1,3-dihydroxyquinolinone derivatives. Unfortunately (Scheme 52) the analogous reaction of the diacyl 2-nitronaphthylidene derivative (197b) with aqueous sodium hypochlorite gave largely (34%) the *trans* benzoyl 2-nitronaphthyloxirane derivative (202) and only a very low yield (3%) of the *cis* isomer (212). The poor yield of the latter prevented the study of its acid- catalysed cyclisation in the presence of hydrogen chloride.

2.3 Studies on the Lewis Acid- catalysed Cyclisation Reactions of 1-Nitronaphth-2-yloxirane Derivatives to 1,3-Dihydro-3-oxonaphth[1,2-c]isoxazoles

As discussed in Chapter 1 (see section 3.2, page 15 and Scheme 13), Lewis acids are known⁵⁰ to catalyse the cyclisation of 2-nitrophenyloxirane derivatives to



(i) SnCl_4 , toluene, room temp.

(ii) Ac_2O , reflux.

(iii) 2M NaOH (aqu.), heat.

(iv) AcCl , Et_3N , dioxane, room temp.

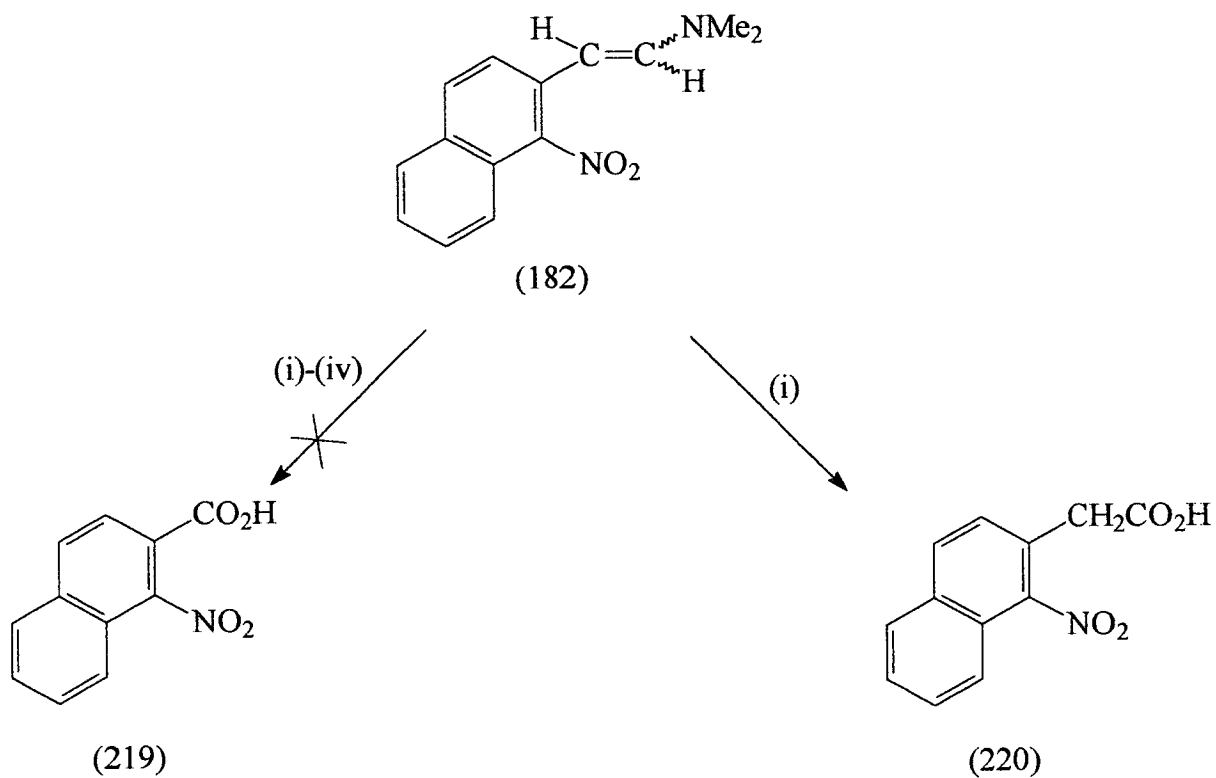
Scheme 53

2,1-benzisoxazoles and/or 2-aminobenzoic acid derivatives. Analogous studies (Scheme 53) of the behaviour of the *trans* benzoyl 2-nitronaphthyloxirane derivative (202) towards Lewis acids are described in the present section.

Initially the reaction of the nitronaphthyloxirane derivative (202) with stannic chloride in toluene was investigated. This reaction gave a moderate yield (47%) of a product whose analytical and spectroscopic properties were in accord with the naphthisoxazole structure (214). The naphthisoxazole derivative (214) failed to undergo acetylation by reaction with acetic anhydride under mild conditions at 100°C, only recovered starting material being recovered under these conditions. In contrast heating this N-substituted naphthisoxazole derivative (214) under reflux with acetic anhydride gave a low yield of a product whose combustion analysis and spectroscopic properties support its formulation as the naphthoxazine derivative (217). The formation of this compound from the naphthisoxazole (214) can be explained on the basis of initial ring- opening to the acyl aminonaphthoic acid derivative (215) dehydration of which promoted by acetic anhydride would afford the naphthoxazine derivative (217). The latter process is analogous to the well known⁸⁵ dehydrative cyclisation of ortho acyl aminobenzoic acids to benzoxazine derivatives.

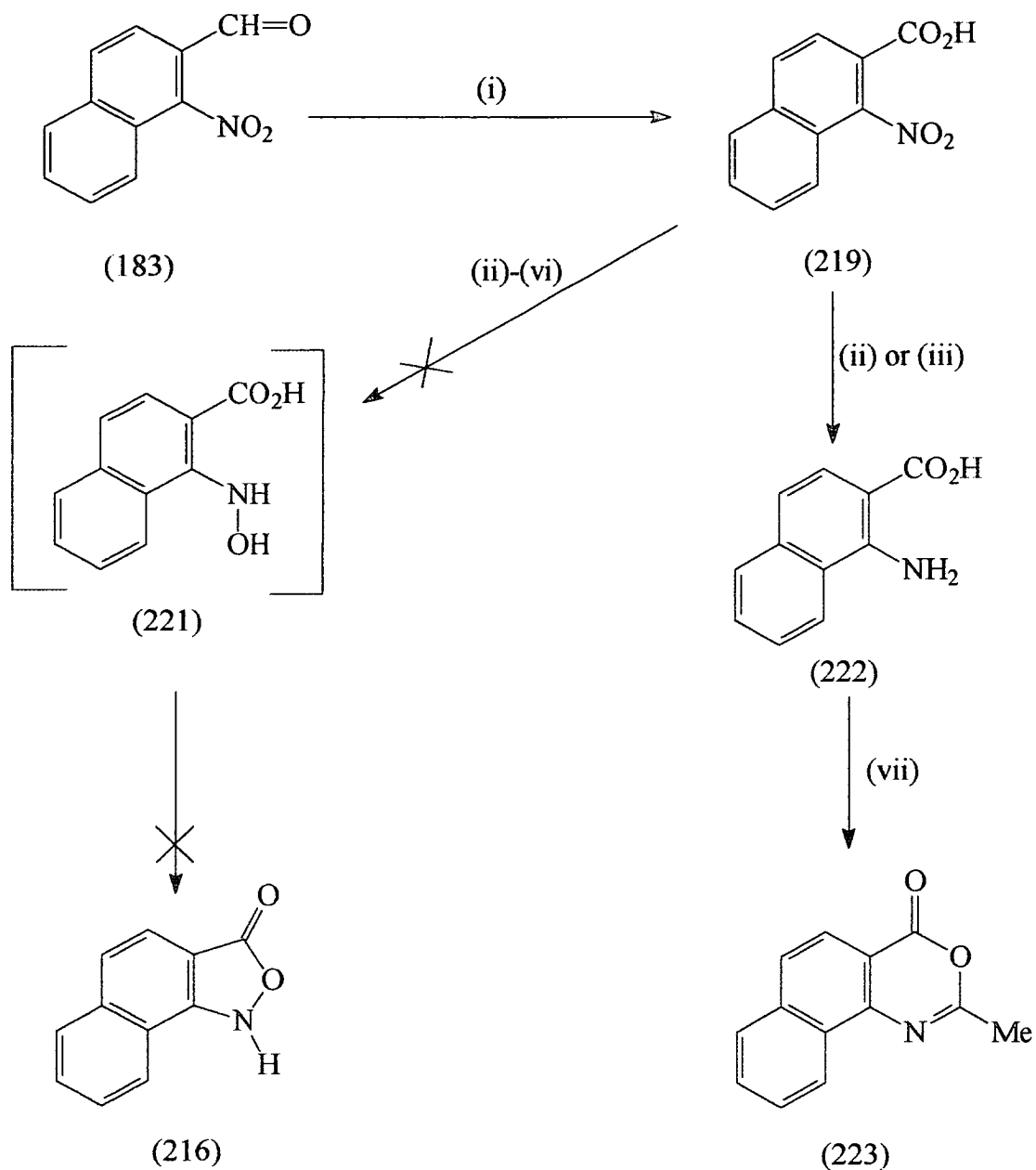
It was found that the N-substituted naphthisoxazole derivative (214) was readily cleaved with 2M aqueous sodium hydroxide solution to afford the expected N-unsubstituted naphthisoxazole derivative (216) in quantitative yield as the only identifiable product. This known⁸⁶ N-unsubstituted naphthisoxazole (216) derivative had combustion analysis and mass, IR and ¹H NMR spectra in good agreement with its structure. However the naphthisoxazole derivative (216) isolated had a melting point (141-143°C) considerably lower than the literature⁸⁶ (193°C). It was therefore imperative to firmly establish the correct structural assignment of the N-unsubstituted naphthisoxazole derivative (216).

Studies were carried out to provide confirmatory proof for the structure of the N-substituted naphthisoxazole derivative (214) by its unambiguous synthesis from



- (i) CrO_3 , AcOH , H_2O , 100°C .
 (ii) NaIO_4 , DME, reflux.
 (iii) NaOCl (aqu.), dioxane, room temp.
 (iv) 30% H_2O_2 (aqu.), 1M NaOH (aqu.), room temp.

Scheme 54



- (i) CrO_3 , AcOH , H_2O , 100°C .
(ii) H_2 , Pd-C , EtOH , *atmos. press.*
(iii) NaBH_4 , Pd-C , MeOH , *room temp.*
(iv) H_2 , *Raney Ni*, DMF , *atmos. press.*
(v) Zn , NH_4Cl , THF , H_2O , $0-5^\circ\text{C}$.
(vi) Zn , NH_4Cl , Ba(OH)_2 , H_2O , $10-20^\circ\text{C}$.
(vii) Ac_2O , *reflux*.

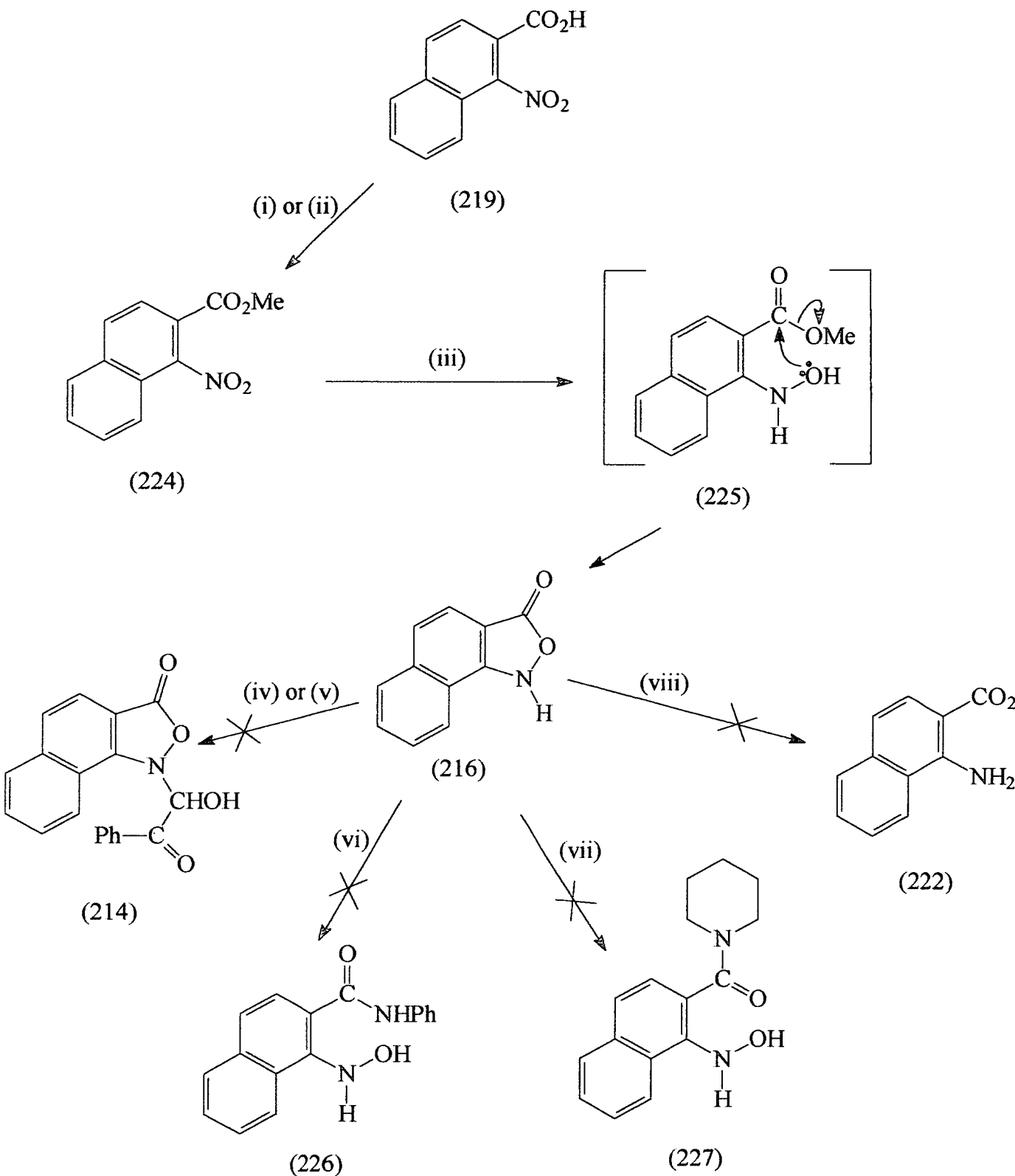
Scheme 55

the N-unsubstituted naphthisoxazole derivative (216) and 2-oxophenylacetaldehyde. Initial work (Scheme 54) involved investigating routes to forming the known⁸⁶ N-unsubstituted naphthisoxazole derivative (216), and in the process confirm the earlier synthesis of the latter derivative. The pathway investigated hinged on the synthesis of 1-nitronaphthalene-2-carboxylic acid (219). It was hoped (Scheme 55) the nitro group of this carboxylic acid derivative (219) would undergo selective reduction to afford a hydroxylamine intermediate (221) subsequent cyclisation of which would give the N-unsubstituted naphthisoxazole derivative (216). In practice (Scheme 54) heating the enamine derivative (182) under reflux with sodium periodate in dimethoxyethane failed to give 1-nitronaphthalene-2-carboxylic acid (219). This reaction only afforded 1-nitro-2-naphthaldehyde in good yield (90%). Other routes were investigated in an attempt to synthesise the nitronaphthoic acid derivative (219). Oxidation of the enamine derivative (182) with chromium trioxide in 70% aqueous glacial acetic acid also failed to afford 1-nitronaphthalene-2-carboxylic acid (219). The product isolated in high yield from the reaction of the enamine with chromium trioxide had mass, IR and ¹H NMR spectra consistent with the acetic acid derivative (220). The enamine derivative (182) was also not converted into the 1-nitronaphthalene-2-carboxylic acid (219) using aqueous sodium hypochlorite solution. Only unreacted starting material was recovered from the reaction. Similarly the enamine derivative (182) could not be converted into the corresponding 1-nitronaphthalene-2-carboxylic acid (219) using 30% aqueous hydrogen peroxide in 1M aqueous sodium hydroxide solution. This reaction gave only unreacted starting material in high yield (96%).

A further attempt to synthesise the nitronaphthoic acid derivative (219) was by oxidation of 2-methyl-1-nitronaphthalene. Unfortunately the oxidation of 2-methyl-1-nitronaphthalene using chromium trioxide in 70% aqueous glacial acetic acid failed to give the naphthoic acid derivative (219) with only unreacted starting material being recovered in high yield. However (Scheme 55) oxidation of 1-nitro-2-naphthaldehyde (183) using chromium trioxide afforded a product in good yield (93%) which had mass, IR and ¹H NMR spectra fully in accord with its formulation as the known 1-nitronaphthalene-2-carboxylic acid (219). The melting point of the isolated product (232-234°C) was also close to the literature⁸⁷ value for

1-nitronaphthalene-2-carboxylic acid (239°C). Confirmation of the carboxylic acid structure (219) was provided by its reduction to the aminonaphthoic acid derivative (222) using hydrogen in the presence of palladium-on-charcoal in ethanol. The reaction resulted in the formation of the known aminonaphthoic acid derivative (222) in high yield (88%) whose combustion analysis and spectroscopic data were consistent with its assigned structure. However the melting point for 1-aminonaphthalene-2-carboxylic acid (185-187°C) was significantly lower than the literature value⁸⁸ (205°C). Confirmation of the aminonaphthoic acid structure (222) was provided by its conversion into the oxazine derivative (223). Heating the aminonaphthoic acid derivative (222) in acetic anhydride under reflux resulted in its smooth conversion into the corresponding oxazine derivative (223) in high yield (81%) whose combustion analysis and mass, IR and ¹H NMR spectra in agreement with its structure. The melting point of the isolated product (179-181°C) was in agreement with the known⁸⁹ melting point (178°C) for the oxazine derivative (223).

Having (Scheme 55) obtained the nitronaphthoic acid derivative (219) attention was drawn to selectively reducing the nitro group of this nitronaphthoic acid derivative to the hydroxylamine derivative which it was hoped would cyclise to the N-unsubstituted naphthisoxazole derivative (216). Unfortunately hydrogenation of 1-nitronaphthalene-2-carboxylic acid (219) in the presence of Raney nickel afforded the aminonaphthoic acid derivative (222) in high yield (74%). Disappointingly the reaction of 1-nitronaphthalene-2-carboxylic acid (219) with zinc and ammonium chloride also failed to give the N-unsubstituted naphthisoxazole derivative (216). Only an intractable solid was isolated from this reaction. Further reduction methods were investigated in an attempt to selectively reduce the nitro group of the nitronaphthoic acid derivative (219) in the expectation of forming the N-unsubstituted naphthisoxazole derivative (216). The reduction of the nitronaphthoic acid derivative (219) using zinc in the presence of ammonium chloride and barium hydroxide proved unsuccessful with the isolation of an intractable solid together with some unreacted starting material. In a final attempt to selectively reduce the nitro group of the nitronaphthoic acid derivative (219), the nitronaphthoic acid derivative (219) was treated with sodium borohydride and palladium-on-charcoal in methanol and this unfortunately failed to give the



- (i) SOCl_2 , 100°C then MeOH, reflux.
(ii) MeOH, H_2SO_4 (conc.), reflux.
(iii) Zn, NH_4Cl , THF, H_2O , $0-5^\circ\text{C}$.
(iv) PhCOCH=O , H_2O , 60°C or dioxane, 50°C .
(v) PhCOCH=O , Et_3N , dioxane, room temp.

- (vi) piperidine, dioxane, room temp.
(vii) aniline, dioxane, reflux.
(viii) H_2 , Pd-C, EtOH, room temp. and atmos. pres.

Scheme 56

N-unsubstituted naphthisoazole derivative (216). Only 1-aminonaphthalene-2-carboxylic acid (222) was isolated in low yield (33%) from this reaction.

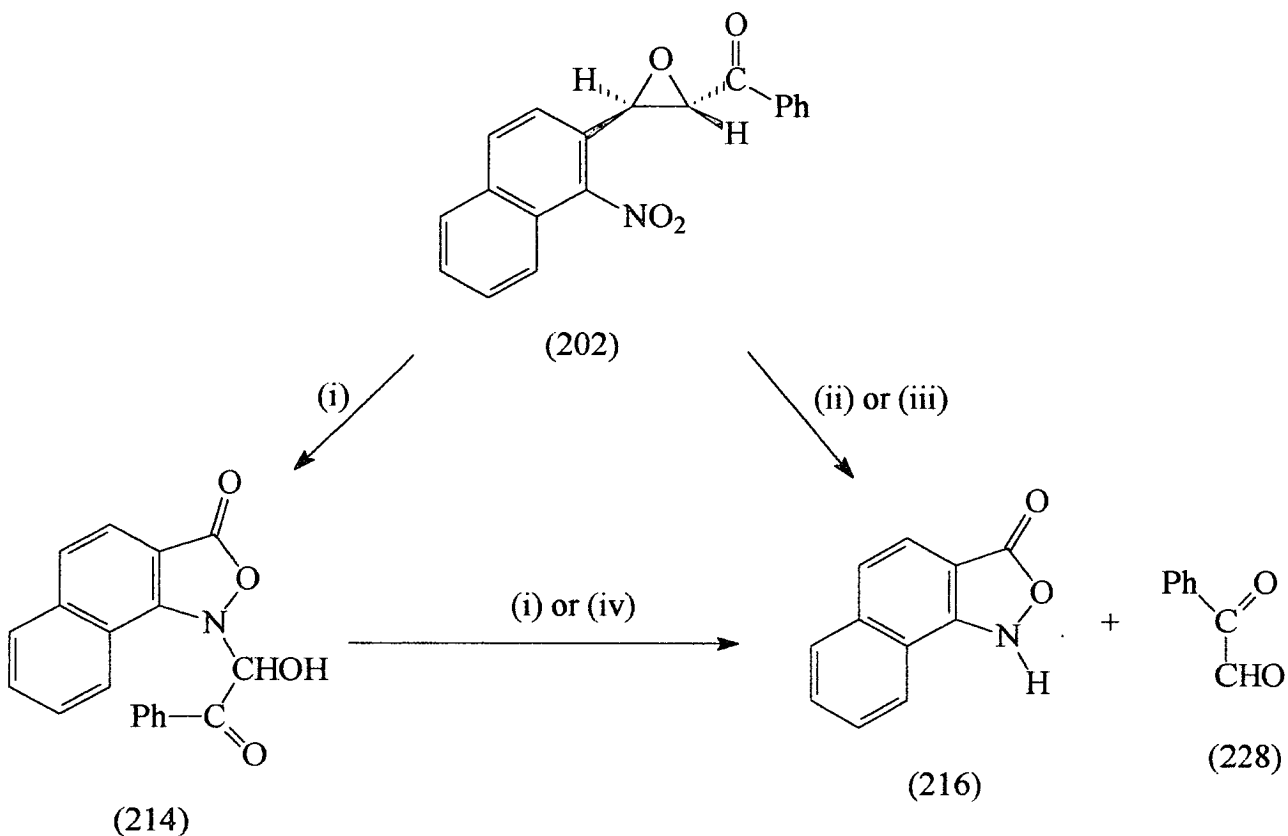
Another pathway (Scheme 56) was investigated to obtain the N-unsubstituted naphthisoazole (216). This route involved the formation of the nitro- ester derivative (224), which may be formed from the nitronaphthoic acid derivative (219). It was thought the nitro ester derivative (224) would be more reactive than the nitronaphthoic acid derivative (219) and undergo reductive cyclisation to afford the N-unsubstituted naphthisoazole derivative (216). The ester group of the nitro ester derivative (224) is a good leaving group and the presence of this leaving group enhances the reactivity of the side- chain to nucleophilic attack by a nucleophile (ie hydroxylamine group in this case). 1-Nitronaphthalene-2-carboxylic acid (219) reacted with thionyl chloride at 100°C followed immediately by heating under reflux in methanol to give the ester derivative (224) in poor yield (11%) which analysed correctly and had spectroscopic properties consistent with its structure. Since this reaction was rather inefficient other conditions were investigated to obtain the ester derivative (224). Heating the nitronaphthoic acid (219) under reflux with concentrated sulfuric acid in methanol gave the ester derivative (224) in excellent yield (78%).

It was found that the methyl ester derivative (224) was readily reduced to the N-unsubstituted naphthisoazole derivative (216) in high yield (83%) using zinc and ammonium chloride. The N-unsubstituted naphthisoazole derivative (216) had a melting point and IR spectrum consistent with a sample obtained before. However the melting point (135-137°C) of the N-unsubstituted naphthisoazolone derivative (216) was significantly lower than the literature value⁸⁶ (193°C). The N-unsubstituted naphthisoazole derivative (216) is formed by reduction of the nitro group in the ester derivative (224) to afford the hydroxylamine intermediate (225). Cyclisation of the hydroxylamine derivative (225) with the loss of methanol accounts for the formation of the N-unsubstituted naphthisoazole derivative (216). Confirmation (Scheme 53) of the structure of the N-unsubstituted naphthisoazole derivative (216) was provided by its reaction with acetyl chloride in the presence of triethylamine

which gave the N-acetyl derivative (218) in good yield (66%). The N-acetyl derivative (218) analysed correctly and had spectroscopic properties consistent with its structure. The acetyl group of the N-acetyl naphthisoxazole derivative (218) was readily cleaved with 2M aqueous sodium hydroxide solution to afford the expected N-unsubstituted naphthisoxazole derivative (216) in quantitative yield as the only identifiable product.

Investigations were carried out on the reactivity of the N-unsubstituted naphthisoxazole derivative (216) with various reagents in the hope of providing further evidence for the correct structural assignment of the N-unsubstituted naphthisoxazolone derivative (216). These reactions were attempts to cleave open the isoxazole ring of the N-unsubstituted naphthisoxazole derivative (216). The N-unsubstituted naphthisoxazole derivative (216) failed to react with aniline when heated under reflux in dioxane. This reaction gave only unreacted starting material. Similarly the reaction of the N-unsubstituted naphthisoxazole derivative (216) with piperidine proved unsuccessful in forming the piperidine derivative (227). Only the starting material was isolated in this reaction. It was also found that the N-unsubstituted naphthisoxazole derivative (216) could not be hydrogenated to the aminonaphthoic acid derivative (222) using palladium-on-charcoal as catalyst. This reaction afforded some unreacted starting material as the only identifiable material.

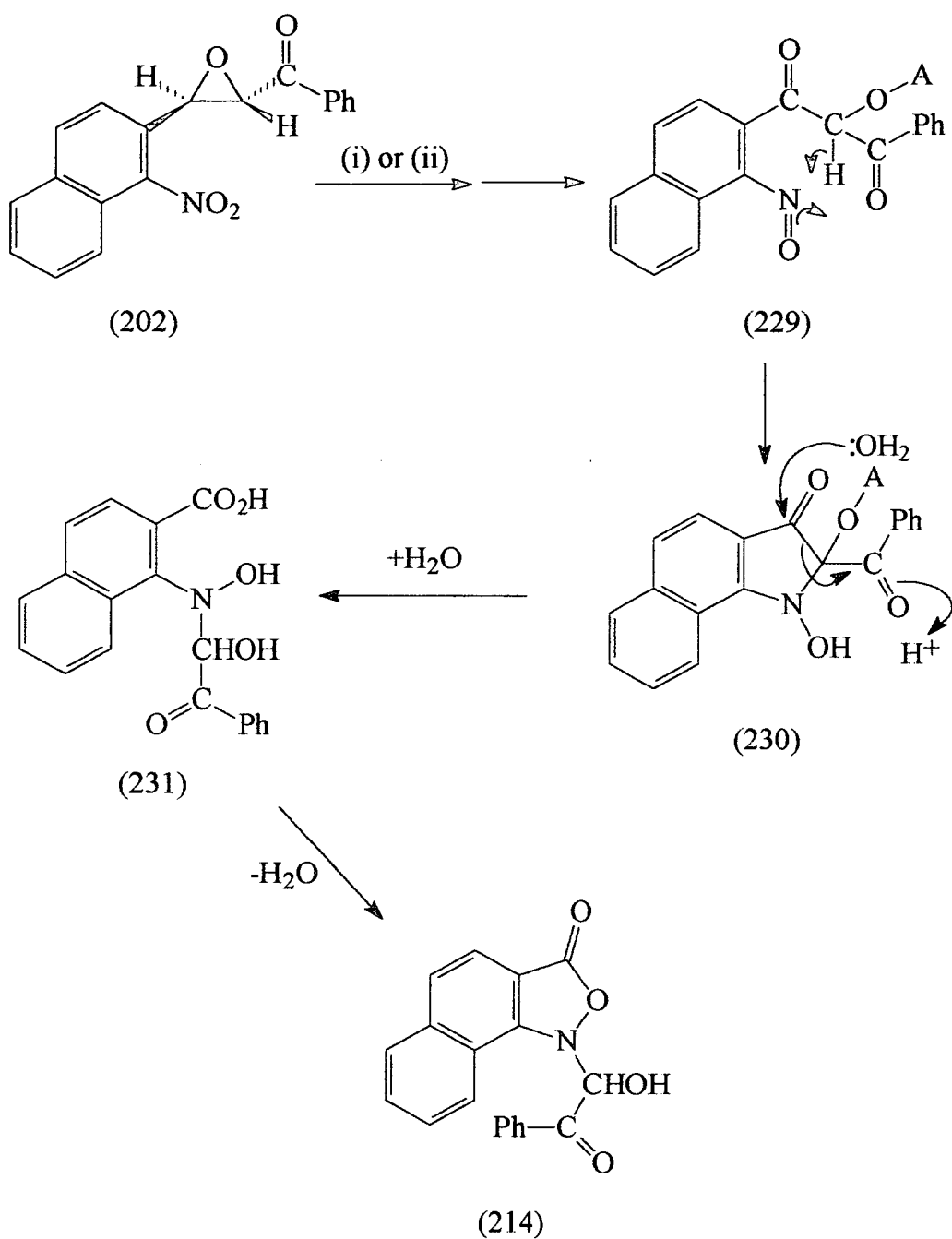
Reactions were carried out (Scheme 56) to prove the structure of the N-substituted naphthisoxazole derivative (214) by the unambiguous synthesis from the N-unsubstituted naphthisoxazole derivative (216) and 2-oxophenylacetaldehyde. Unfortunately the N-unsubstituted naphthisoxazole derivative (216) failed to react with 2-oxophenylacetaldehyde in water at 60°C, the reaction affording only unreacted N-unsubstituted naphthisoxazolone derivative (216). Similarly the N-unsubstituted naphthisoxazole derivative (216) was recovered largely unchanged after heating in dioxane at 50°C with 2-oxophenylacetaldehyde. Also disappointing was the reaction of the N-unsubstituted naphthisoxazole derivative (216) with 2-oxophenylacetaldehyde using triethylamine as the catalyst in dioxane. The N-unsubstituted naphthisoxazole derivative (216) was recovered unchanged in this reaction.



- (i) $\text{BF}_3 \cdot \text{Et}_2\text{O}$, DME, reflux.
(ii) $\text{BF}_3 \cdot \text{Et}_2\text{O}$, DME, room temp.
(iii) $\text{BF}_3 \cdot \text{Et}_2\text{O}$, DCM, room temp or reflux.
(iv) silicagel, DCM.

Scheme 57

Investigations (Scheme 57) were carried out to study the effects of other Lewis acids on the *trans* naphthyloxirane derivative (202) in the hope of forming the novel N-substituted naphthisoxazole derivative (214). However the *trans* naphthyloxirane derivative (202) reacted with stannic chloride in dichloromethane to afford the N-unsubstituted naphthisoxazole derivative (216) in good yield (65%) together with a small quantity of 2-benzoyl-4-oxo-4H-naphth[1,2-d]-1,3-oxazine (217). The formation of this latter product is discussed later. The *trans* naphthyloxirane derivative (202) was also transformed into the N-substituted naphthisoxazole derivative (214) in poor yield (32%) when heated under reflux with boron trifluoride etherate in dimethoxyethane. It was thought that carrying out the boron trifluoride catalysed cyclisation reaction of the *trans* naphthyloxirane derivative (202) to the N-substituted naphthisoxazolone derivative (214) at elevated temperature may be leading to the thermal breakdown of the N-substituted naphthisoxazolone derivative (214) to the N-unsubstituted naphthisoxazole derivative (216). However repeating the reaction at room temperature afforded unreacted naphthyloxirane derivative (202) in moderate yield (50%) together with the N-unsubstituted naphthisoxazole (216) in low yield (18%). The *trans* naphthyloxirane derivative (202) also reacted with boron trifluoride etherate in dichloromethane instead of dimethoxyethane to give the N-unsubstituted naphthisoxazole derivative (216) and 2-oxophenylacetaldehyde (228) each in high yields. Repeating this reaction at elevated temperature gave a mixture whose IR spectrum resembled that of the N-substituted naphthisoxazole derivative (214). However column chromatography of the mixture gave the N-unsubstituted naphthisoxazole derivative (216) and 2-oxophenylacetaldehyde (228) each in good yield. It was thought that the side chain of the N-substituted naphthisoxazole derivative (214) may be highly prone to cleavage using a suitable acid catalyst. The steric bulk (naphthalene ring) in proximity to the side chain of the N-substituted naphthisoxazolone derivative (214) may promote the side-chain - naphthisoxazole bond dissociation under certain conditions. It was found that the side-chain of the N-substituted naphthisoxazole derivative (214) could be readily cleaved with just silicagel in dichloromethane to afford the N-unsubstituted naphthisoxazole derivative (216) and 2-oxophenylacetaldehyde (228) each in good yields.



- (i) SnCl_4 , toluene or DCM, room temp.
(ii) $\text{BF}_3 \cdot \text{Et}_2\text{O}$, DME, reflux.

Scheme 58

As discussed earlier (see Chapter 2, section 4, page 53 and Scheme 37)

2,1-benzisoxazoles undergo rearrangement to 2-aminobenzoic acid derivatives using boron trifluoride etherate. However heating the N-substituted naphthisoxazole derivative (214) under reflux with boron trifluoride etherate in dimethoxyethane failed to undergo a similar rearrangement reaction. Instead some unreacted starting material was isolated from the reaction together with a dark brown oil which after column chromatography gave the N-unsubstituted naphthisoxazole derivative (216) in low yield (38%).

The mechanism (Scheme 58) of formation of the N-substituted naphthisoxazole derivative (214) is thought to be similar to that discussed earlier involving the Lewis acid catalysed cyclisation of nitrophenyloxiranes to 2,1-benzisoxazolones (see Chapter 1, section 3.1, page 16 and Scheme 14). The Lewis acid is thought to draw electron density away from the side- chain in the *trans* naphthyloxirane derivative (202) which then becomes more electrophilic and prone to nucleophilic attack by the adjacent nitro group. This leads to the initial *trans* naphthyloxirane derivative (202) being converted into the nitrosonaphthyl intermediate (229), subsequent cyclisation of which gives the cyclic naphthalene intermediate (230). On work up of the reaction mixture in water, the cyclic naphthalene intermediate reacts with water to afford the naphthoic acid intermediate (231). Cyclisation of the latter intermediate (231) with the loss of water accounts for the formation of the isolated naphthisoxazole derivative (214). However cyclisation of the naphthoic acid intermediate (231) via the methylene hydroxyl group with the loss of water would give 2-benzoyl-4-oxo-4H-naphth[1,2-d]-1,3-oxazine (217)(see earlier).

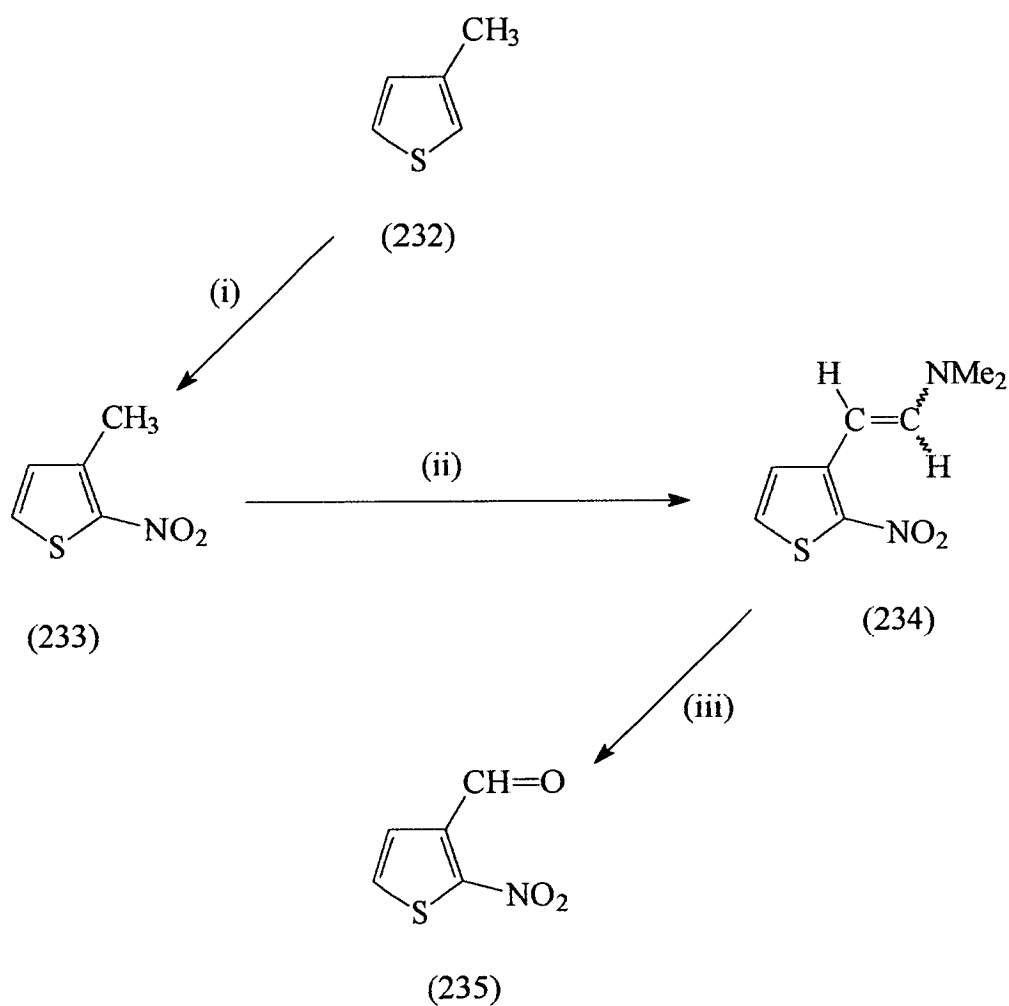
2.4 CONCLUSIONS AND FUTURE WORK

It was found (Scheme 45) that the nitronaphthaldehyde (183) failed to react with diacylmethane derivatives (136) in the presence of hydrogen chloride to give the N-hydroxybenzoquinolinone derivatives (184). However preforming the nitronaphthylidene derivatives (197) [proposed to be intermediates in the formation of N-hydroxybenzoquinolinone derivatives (184) by the hydrogen chloride catalysed

reaction of the nitronaphthaldehyde (183) with diacylmethane derivatives (136)] and treating these derivatives with hydrogen chloride gave the N-hydroxybenzoquinolinone derivatives (184) in excellent yields. Future work will involve investigating other ways of obtaining the nitronaphthylidene derivatives in high yields which would then be expected to cyclise to give the corresponding N-hydroxybenzoquinolinone derivatives in the presence of hydrogen chloride.

It was noted (Scheme 47) that the *trans* naphthyloxirane derivative (200; $R^1=Ph$; $R^2=H$) failed to cyclise using hydrogen chloride as the catalyst to the novel 1,3-dihydroxybenzoquinolinone (200; $R^3=Ph$). Instead (Scheme 48) this inefficient reaction gave the novel naphthisoxazole derivative (204) in low yield. *Cis* nitrophenyloxirane derivatives are known^{68,69} to readily undergo cyclisation in the presence of hydrogen chloride to the N-hydroxyquinolinones. Future work will involve finding routes to nitronaphthyloxirane derivatives which contain a *cis* acyl group. It is thought that *cis* nitronaphthyloxirane derivatives would cyclise to novel N-hydroxybenzoquinolinones derivatives when using hydrogen chloride as the catalyst.

Studies (Scheme 53) carried out on the *trans* naphthyloxirane derivative (202) showed that it was converted into the N-substituted naphthisoxazole derivative (214) in the presence of a Lewis acid. Attempts were made to confirm the N-substituted naphthisoxazole structure (214) by its unambiguous synthesis from the N-unsubstituted naphthisoxazole derivative (216) and 2-oxophenylacetaldehyde. Future work will involve finding other ways of forming the N-substituted naphthisoxazole derivative (214) to confirm its structure. Also further studies will be carried out on the reactions of the N-unsubstituted naphthisoxazole derivative (216) and hence confirm its structure. Investigations may also be made on obtaining the *cis* naphthyloxirane derivative (212) so as to study its cyclisation to the N-substituted naphthisoxazole derivative (214) in the presence of a Lewis acid.

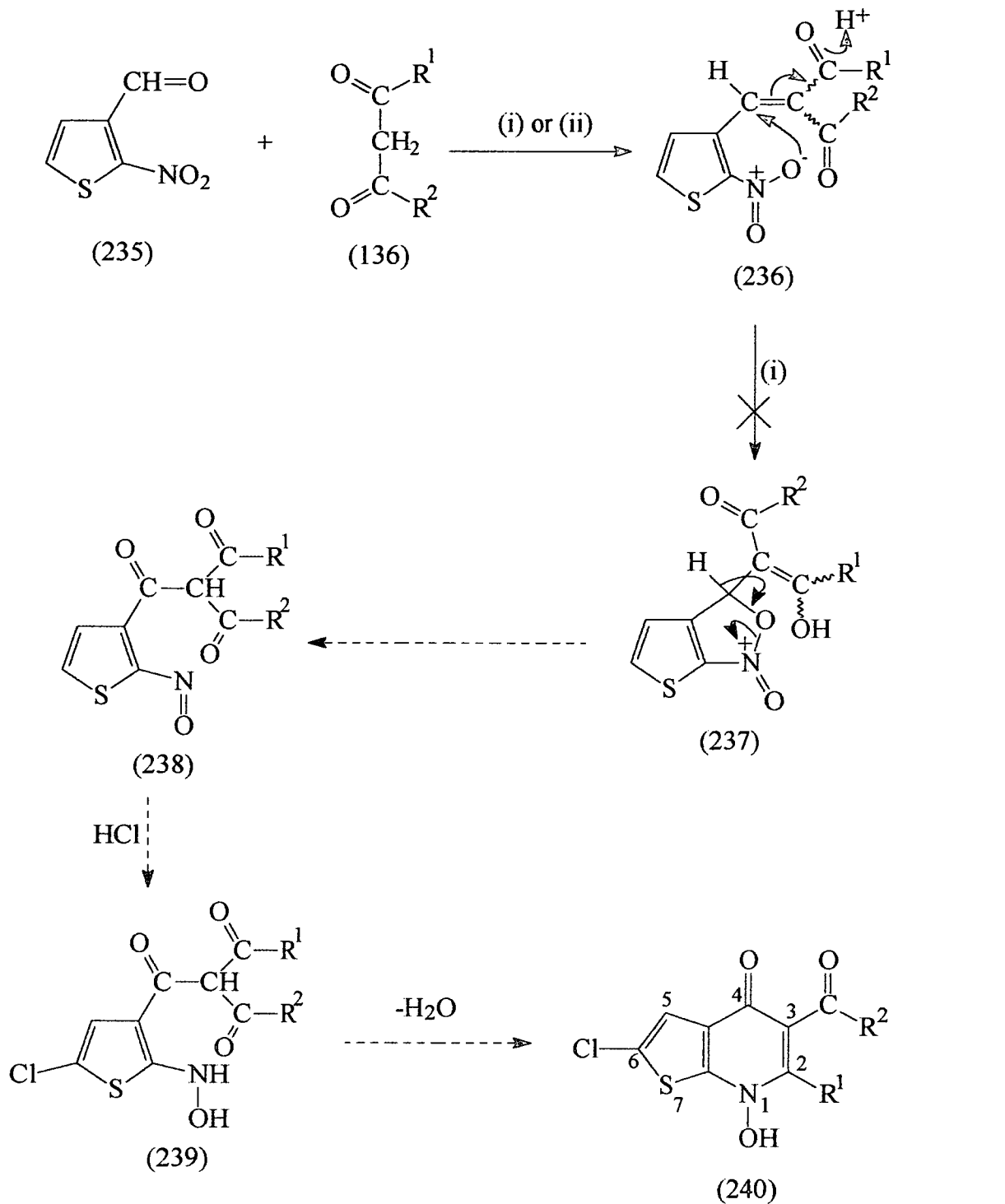


(i) HNO_3 , Ac_2O , 0°C .

(ii) $\text{Me}_2\text{NCH}(\text{OMe})_2$, DMF, reflux.

(iii) NaIO_4 , THF, H_2O , room temp.

Scheme 59



	\underline{R}^1	\underline{R}^2
a;	Me	Me
b;	Me	Ph
c;	Ph	Ph
d;	Me	OEt

(i) $HCl_{(g)}$, ether, $0^\circ C$.

(ii) piperidine, EtOH or AcOH, room temp. or reflux.

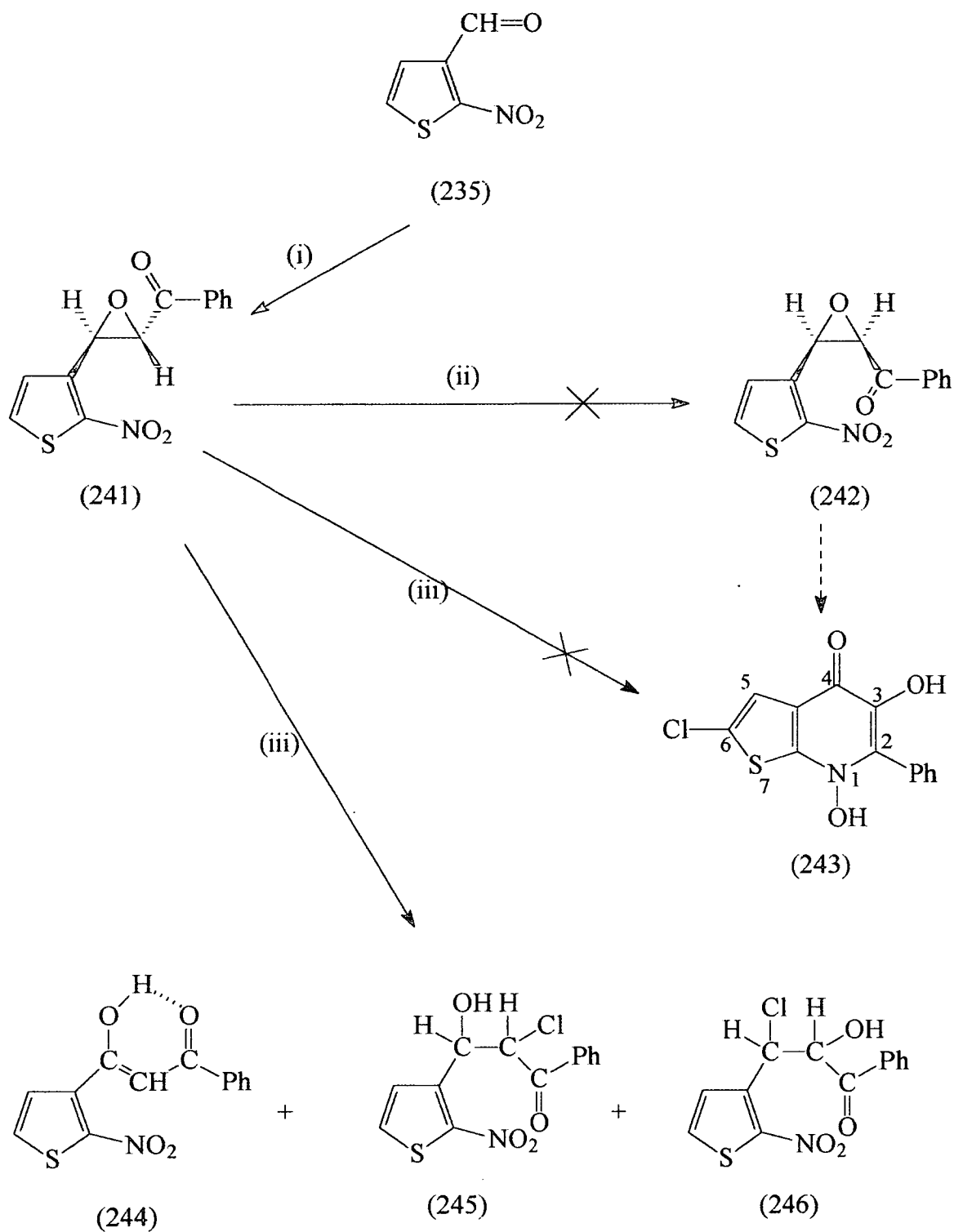
Scheme 60

3. STUDIES ON THE SYNTHESIS OF N-HYDROXY THIENO[2,3-b]PYRIDINONES BY ACID- CATALYSED CYCLISATION REACTIONS OF ORTHO- SUBSTITUTED NITROTHIOPHENE DERIVATIVES

3.1 Studies on the Attempted Acid- catalysed Cyclisation Reactions of 2-Nitro-3-nitrothienylidene Derivatives to 1-Hydroxy-4-thieno[2,3-b]pyridinones

With a view to further extending the novel acid- catalysed cyclisation reactions of nitroaromatic derivatives to otherwise inaccessible N-hydroxy heterocycles, attention was next turned to the study of the acid- catalysed cyclisation reactions of nitrothienyl derivatives to N-hydroxythienopyridinones. The general strategy (Scheme 59) involved synthesising 2-nitrothiophene-3-carboxaldehyde (235) which could then be condensed (Scheme 60) with an active diacylmethane derivative (136) in the presence of an acid catalyst to afford a N-hydroxythienopyridinone (240). Initially 2-nitrothiophene-3-carboxaldehyde (235) was synthesised in several steps [(232)→(233)→(234)→(235)] from 3-methylthiophene (232). 3-Methylthiophene (232) was nitrated using a known method⁹⁰ to afford 3-methyl-2-nitrothiophene (233) in moderate yield (53%). Heating 3-methyl-2-nitrothiophene (233) with N,N-dimethylformamide dimethyl acetal under reflux in dimethoxyethane gave a product in high yield (89%) which had mass, IR and ¹H NMR spectra in good agreement with its formulation as the enamine derivative (234). The enamine derivative (234) was converted into the known⁹¹ 2-nitrothiophene-3-carboxaldehyde (235) in good yield using sodium periodate in aqueous tetrahydrofuran.

The reaction (Scheme 60) of 2-nitrothiophene-3-carboxaldehyde (235) with pentane-2,4-dione (136a) in ethereal hydrogen chloride was investigated and failed to give the N-hydroxythienopyridinone (240). Instead the reaction gave a product in high yield (84%) whose combustion analysis and spectroscopic properties were in agreement with the nitrothienylidene structure (236a). In light of this result investigations were carried out into the condensation reactions of 2-nitrothiophene-3-carboxaldehyde (235) with other active diacylmethane derivatives (136) in the presence of hydrogen chloride. Carrying out the reaction using 1-phenylbutane-1,3-dione (136b) as the active diacylmethane derivative gave the corresponding nitrothienylidene derivative



- (i) PhCOCH_2Br , NaOMe, MeOH, room temp.
 (ii) NaOMe, MeOH, room temp.
 (ii) $\text{HCl}_{(g)}$, DME or dioxane, 0°C or 11°C .

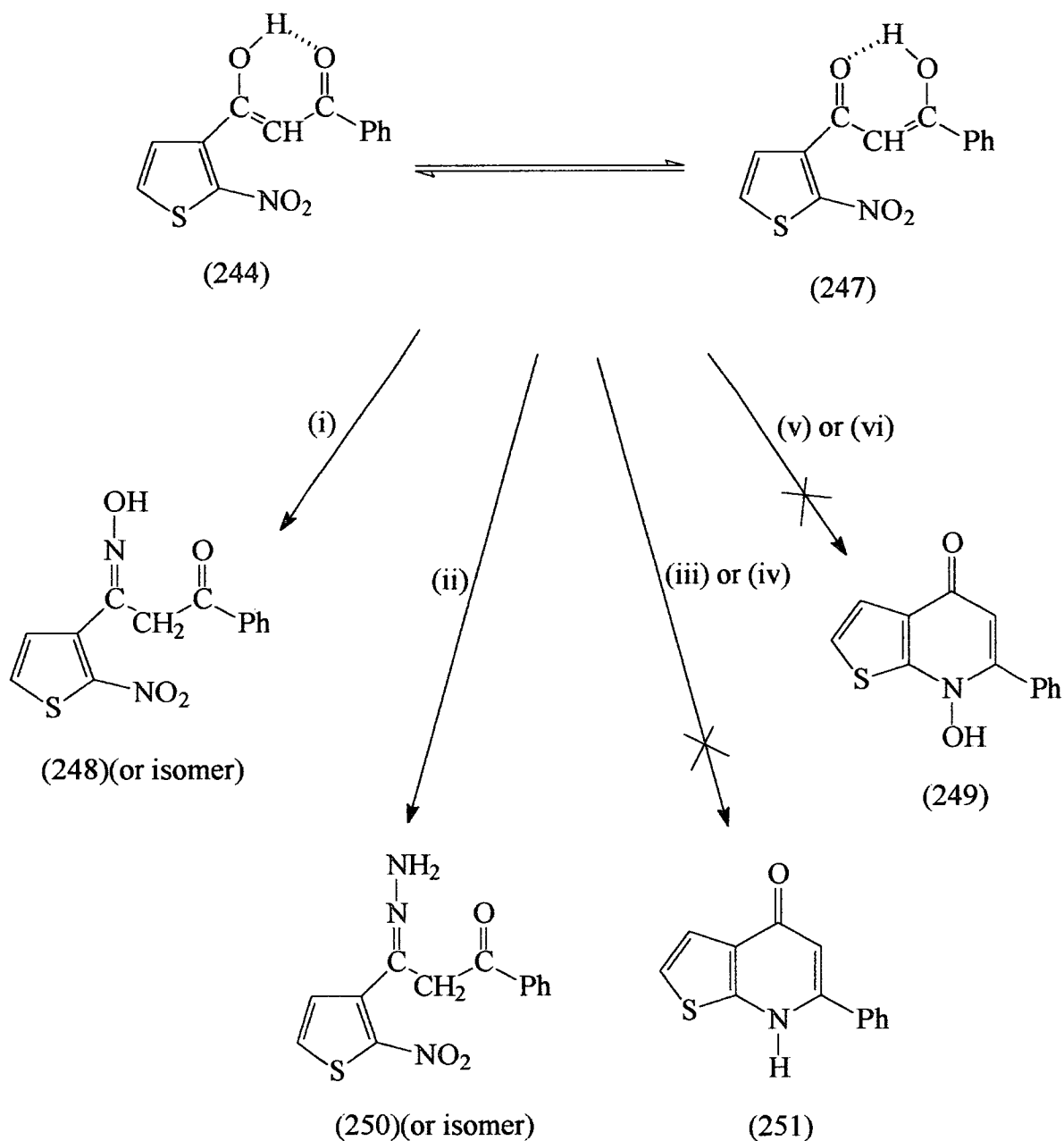
Scheme 61

(236b) in excellent yield which analysed correctly and had spectroscopic data fully in accord with its assigned structure. In contrast the reaction of 2-nitrothiophene-3-carboxaldehyde (235) with 1,3-diphenylpropane-1,3-dione (136c) in ethereal hydrogen chloride failed, with unreacted 2-nitrothiophene-3-carboxaldehyde (235) being isolated as the only identifiable material.

It was found that 2-nitrothiophene-3-carboxaldehyde (235) reacted with ethyl 3-oxobutanoate (136d) in ethereal hydrogen chloride to give a partially separated *E* and *Z* isomeric mixture of the nitrothienylidene derivative (236d) in good yield (80%) which were identified by combustion analyses and spectroscopic data. This reaction failed to give the expected N-hydroxythienopyridinone (240d). The apparent lack of reactivity of the nitrothienylidene derivatives (236) to undergo acid- catalysed cyclisation reactions to the N-oxygenated thienopyridinones (240) is attributed to the slow nucleophilic attack by the nitro group of the nitrothienylidene derivative on the ortho side- chain [(236)→(237)→(238)→(239)→(240)] to ultimately give the thienopyridinone derivative (240). This mechanism is based on work discussed earlier (Chapter 1, section 3.2, page 18 and Scheme 20) where benzylidene derivatives undergo hydrogen chloride catalysed cyclisation reactions to N-hydroxyquinolinones.

3.2 Studies on the Attempted Acid- catalysed Cyclisation Reactions of 2-Nitrothien-3-yloxirane Derivatives to 1,3-Dihydroxy-4-thieno[2,3-b]pyridinones

Attention was turned (Scheme 61) to synthesising the nitrothienyloxirane derivative (241) which was thought to be more reactive than the nitrothienylidene derivatives (236) with regard to undergoing acid- catalysed cyclisation to a N-oxygenated thienopyridinone. The oxirane ring of the nitrothienyloxirane derivative (241) is a built-in leaving group which makes the side- chain susceptible to nucleophilic attack by an adjacent nitro group. Initial work in this area involved forming the *trans* nitrothienyloxirane derivative (241) from the 2-nitrothiophene-3-carboxaldehyde (235) and 2-bromoacetophenone. In practice 2-nitrothiophene-3-carboxaldehyde (235) reacted readily with 2-bromoacetophenone in methanolic sodium methoxide to



- (i) $\text{NH}_2\text{OH} \cdot \text{HCl}$, Na_2CO_3 , EtOH, room temp.
 (ii) NH_2NH_2 , EtOH, reflux.
 (iii) H_2 , Pd-C, EtOH, room temp, atmos.press.
 (iv) SnCl_4 , HCl (aqu.), THF, reflux.
 (v) H_2 , Raney Ni, DMF, room temp, atmos.press.
 (vi) NaBH_4 , Pd-C, NaOH, H_2O , room temp.

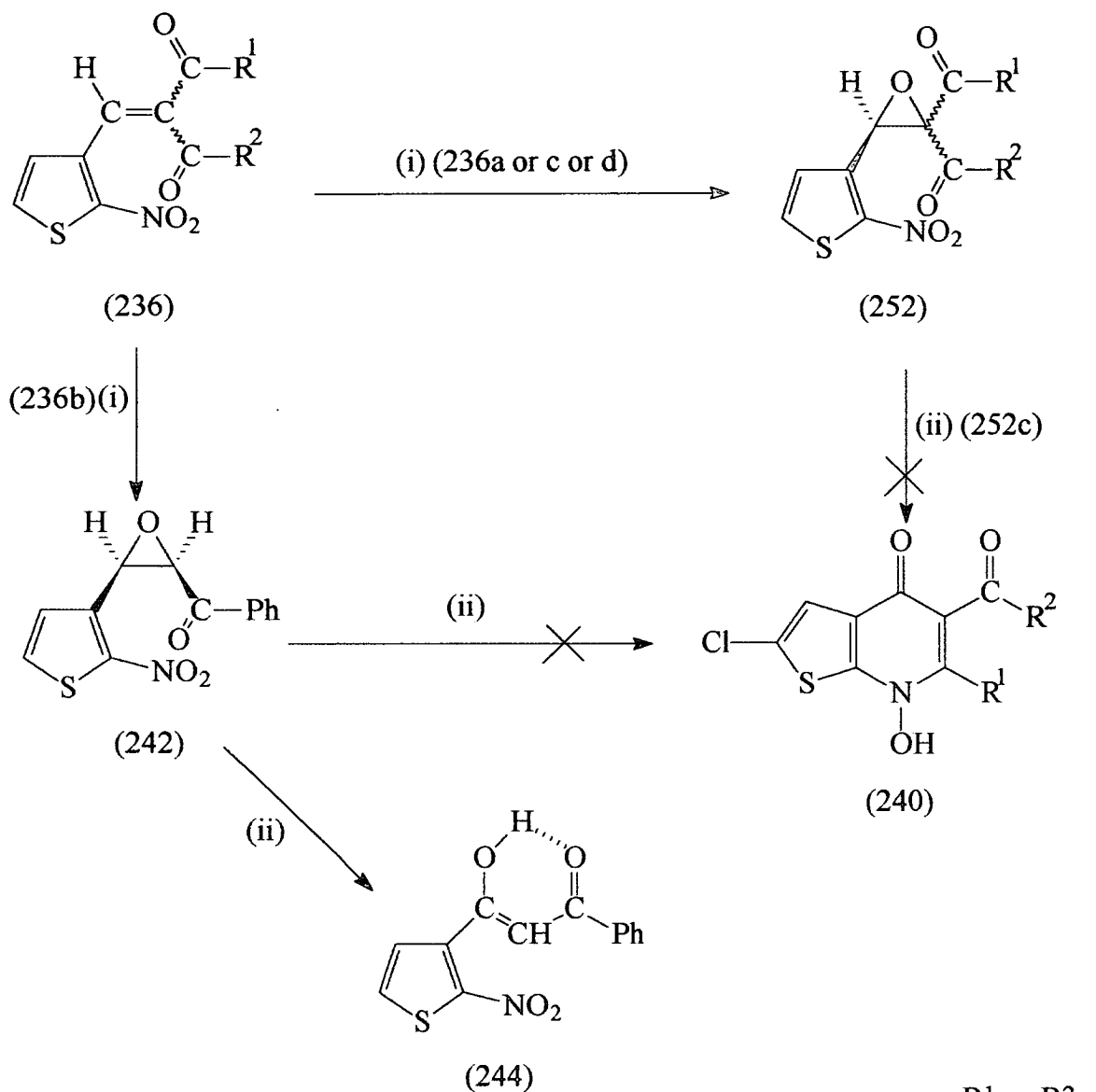
Scheme 62

afford the *trans* nitrothienyloxirane derivative (241) in good yield (80%) whose combustion analysis and spectroscopic properties were consistent with its structure.

Disappointingly treating the *trans* nitrothienyloxirane derivative (241) with hydrogen chloride in dimethoxyethane failed to afford the corresponding 1,3-dihydroxythienopyridinone (243). Instead the reaction gave three products, one of which was isolated in low yield (24%) whose combustion analysis and mass, IR, ^1H and ^{13}C NMR spectra were in agreement with the 1,3-diketone derivative (244). A band at 3344 cm^{-1} (hydroxy group) in the IR spectrum together with the ^{13}C spectrum of the 1,3-diketone derivative (244) suggested (Scheme 62) it existed as two keto-enol tautomers (244) and (247). The second product isolated in low yield (15%) from the reaction of the nitrothienyloxirane derivative (241) with hydrogen chloride analysed correctly and had spectroscopic data in agreement with the formula $\text{C}_{13}\text{H}_{10}\text{ClNO}_4\text{S}$. This formula aided the products tentative assignment as the chlorohydrin derivative (245). The third product also isolated in poor yield (20%) from the hydrogen chloride catalysed reaction had combustion analysis and mass, IR and ^1H NMR spectra consistent with the formula $\text{C}_{13}\text{H}_{10}\text{ClNO}_4\text{S}$, which was tentatively given the isomeric chlorohydrin structure (246). The isomeric chlorohydrin derivatives (245) and (246) were assigned based upon the chemical shifts in the ^1H NMR spectra. It was proposed that in the chlorohydrin derivative (246) the proton geminal to the halogen atom would be deshielded more (by the chloride atom and the nitro group in the nitrothienyl ring) than in the other proposed chlorohydrin derivative (245). The ^1H NMR spectra of these two chlorohydrin derivatives (245) and (246) had significantly different chemical shifts (δ 6.29 ppm and δ 5.77 ppm) for the protons geminal to the halogen atom. However it cannot be completely excluded that the chlorohydrin derivatives (245) and (246) isolated may in fact be diastereomers. Further extensive work is necessary to evaluate the exact configuration of these two chlorohydrin derivatives (245) and (246). Changing the solvent for the reaction of the nitrothienyloxirane derivative (241) with hydrogen chloride also failed to give the N-hydroxythienopyridinone (243). The *trans* nitrothienyloxirane derivative (241) reacted with hydrogen chloride in dioxane to give the 1,3-diketone derivative (244) and the chlorohydrin derivative (245) each in low yields.

Attempts (Scheme 62) were made to chemically prove the structure of the 1,3-diketone derivative (244). The 1,3-diketone derivative (244) reacted with hydroxylamine to give the mono-oxime derivative (248)(or isomer) whose combustion analysis and mass, IR and ^1H NMR spectra were fully in accord with its structure. Also heating the 1,3-diketone derivative (244) with hydrazine under reflux in ethanol gave a product in low yield (30%) which had accurate mass, IR and ^1H NMR spectra consistent with the hydrazine structure (250)(or isomer). 1,3-Dicarbonyl compounds are known⁹² to couple with benzenediazonium chloride. However the 1,3-diketone derivative (244) failed to react with benzenediazonium chloride, only the unreacted nitrothienyl derivative (244) being isolated from the reaction. Evidence for the 1,3-diketone derivative (244) was attempted to be obtained from the oxidative degradation of the 1,3-diketone derivative (244) using chromium trioxide. Disappointingly the 1,3-diketone derivative (244) reacted with chromium trioxide in glacial acetic acid at 100°C to give only a negligible amount of material.

Further evidence was sought to firmly establish the structure of the 1,3-diketone derivative (244). Bands at 1517 and 1376 cm^{-1} in the IR spectrum of the 1,3-diketone derivative (244) suggested the presence of a nitro group within the molecule. Attempts were made to selectively reduce the nitro group of the 1,3-diketone derivative (244) to obtain a hydroxylamine intermediate which it was hoped would cyclise to the novel thienopyridinone (249) or (251). Hydrogenating the 1,3-diketone derivative (244) in the presence of palladium-on-charcoal failed to give the thienopyridinone (251). This reaction only afforded unreacted starting material. Repeating the hydrogenation of the 1,3-diketone derivative (244) using Raney nickel as the catalyst in dimethylformamide produced only an intractable gummy brown solid. Further attempts to selectively reduce the nitro group of the 1,3-diketone derivative (244) also failed. Heating the nitrothiophene derivative (244) with a solution of stannic chloride in 2M aqueous hydrochloric acid under reflux afforded only an intractable solid. Similarly reduction of the nitrothiophene derivative (244) in aqueous sodium hydroxide solution using palladium-on-charcoal and sodium borohydride also failed to give the thienopyridinone (249). This reaction produced only an intractable solid.



	$\underline{R^1}$	$\underline{R^2}$
a;	Me	Me
b;	Me	Ph
c;	Ph	Ph
d;	Me	OEt

(i) NaOCl (aqu.), dioxane or pyridine, room temp.
 (ii) HCl(g), DME, 0°C.

Scheme 63

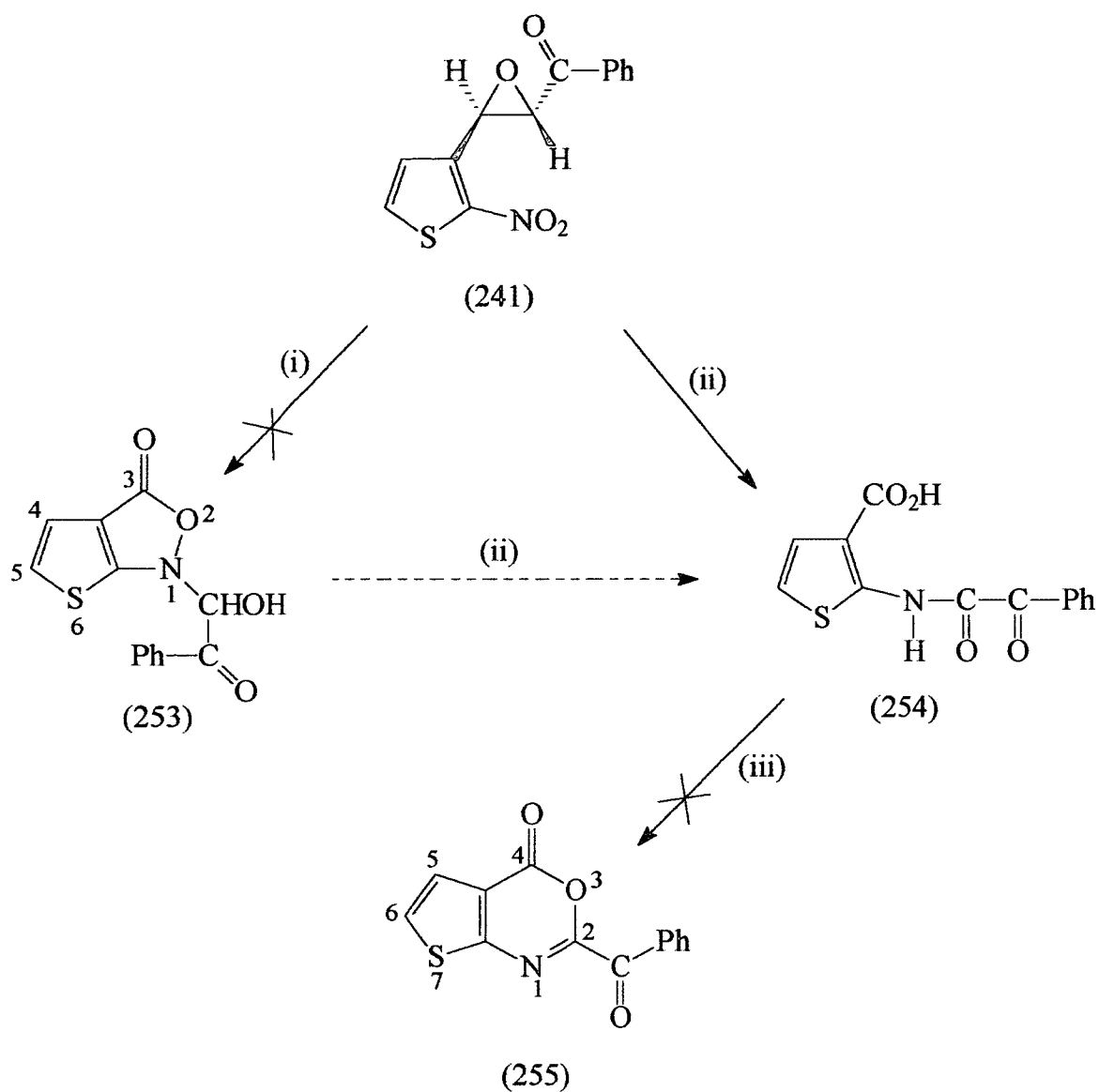
Previous work (see Chapter 1, section 3.2, page 19 and Scheme 21) had shown that *cis* nitrophenyloxirane derivatives readily undergo acid- catalysed cyclisation to N-oxygenated quinolinones. The strategy (Scheme 61) was then changed and an attempt was made to obtain the *cis* nitrothienyloxirane derivative (242). The *cis* nitrothienyloxirane derivative (242) would hopefully lead to the formation of the novel N-hydroxythienopyridone (243) in the presence of hydrogen chloride. Unfortunately the epimerisation of the *trans* nitrothienyloxirane derivative (241) with methanolic sodium methoxide at room temperature failed. Only an intractable dark red oil was recovered from the reaction.

Benzylidene derivatives can easily be converted into the corresponding oxirane derivatives using aqueous sodium hypochlorite solution as described earlier (see Chapter 2, section 3, page 40 and Scheme 34). A similar approach (Scheme 63) was investigated of converting the nitrothienylidene derivatives (236) into the nitrothienyloxirane derivatives (252). Initially (Scheme 60) the nitrothienylidene derivatives (236) were pre-formed by condensing the 2-nitrothiophene-3-carboxaldehyde (235) with an appropriate active diacylmethane compound (136). These nitrothienylidene derivatives (Scheme 63) could then be transformed into the diacyl oxirane derivatives (252). It was expected that the nitrothienyloxirane derivatives (252) would cyclise in the presence of hydrogen chloride to the novel 1,3-dihydroxythienopyridinone derivatives (240). Heating 2-nitrothiophene-3-carboxaldehyde (235) with pentane-2,4-dione (136a) in the presence of piperidine under reflux in ethanol and glacial acetic acid gave the nitrothienylidene derivative (236a) in low yield (6%). This nitrothienylidene derivative (236a) had already been prepared earlier from the condensation of the 2-nitrothiophene-3-carboxaldehyde (235) with pentane-2,4-dione (136a) using hydrogen chloride as the catalyst. Disappointingly the reaction of the nitrothienylidene derivative (236a) with aqueous sodium hypochlorite solution in dioxane failed to give the diacyloxirane derivative (252a), instead the reaction gave an intractable dark red oil.

In contrast (Scheme 63) with the diacetyl substituted nitrothienylidene derivative (236a), the benzoyl substituted nitrothienylidene derivative (236b) was not converted

into the corresponding diacyl substituted nitrothienyloxirane derivative (252b) using aqueous sodium hypochlorite solution in pyridine. Only unreacted starting material was isolated from the reaction. However treating the nitrothienylidene derivative (236b) with aqueous sodium hypochlorite solution in dioxane gave the *cis* nitrothienyloxirane derivative (242) in quantitative yield which had combustion analysis and mass, IR and ^1H NMR spectra consistent with its assigned structure. The synthesis of the *cis* nitrothienyloxirane derivative (242) provided an opportunity to investigate its behaviour to intramolecular cyclisation to the N-hydroxy thienopyridinone (240) in the presence of an acidic catalyst. It was found that treating the *cis* nitrothienyloxirane derivative (242) with hydrogen chloride failed to give the 1,3-dihydroxythienopyridinone (240). In comparison with the *trans* nitrothienyloxirane derivative (241) under the same acidic reaction conditions, the *cis* thienyloxirane derivative (242) reacted with hydrogen chloride to afford the 1,3-diketone derivative (244) in high yield (84%).

Investigations were carried out to see if other diacyl substituted nitrothienyloxirane derivatives (252) would undergo acid- catalysed cyclisation to N-hydroxy heterocycles (240). It was found that (Scheme 60) 2-Nitrothiophene-3-carboxaldehyde (235) reacted smoothly with 1,3-diphenylpropane-1,3-dione (136c) in the presence of piperidine in glacial acetic acid to afford the corresponding nitrothienylidene derivative (236c) in high yield (77%) whose combustion analysis and spectroscopic properties were fully in accord with its structure. The nitrothienylidene derivative (236c) failed to be converted into the nitrothienyloxirane derivative (252c) using aqueous sodium hypochlorite solution in pyridine. Only the unreacted nitrothienyl derivative (236c) was recovered from this reaction. However the nitrothienylidene derivative (236c) reacted readily with aqueous sodium hypochlorite solution in dioxane (instead of pyridine) to afford the diacyl substituted nitrothienyloxirane derivative (252c) in high yield (86%). The nitrothienyloxirane derivative (252c) had combustion analysis and mass, IR and ^1H NMR spectra in good agreement with its assigned structure. Disappointingly though the treatment of the diacyl substituted nitrothienyloxirane derivative (252c) with hydrogen chloride failed to give any of the expected N-hydroxythienopyridinone (240c). This reaction afforded only unreacted starting material. Attempts (Scheme 63) were made to obtain



- (i) SnCl_4 , toluene or DCM, room temp. or 0°C .
(ii) $\text{BF}_3 \cdot \text{Et}_2\text{O}$, DME, room temp. or 50°C or reflux.
(iii) Ac_2O , reflux.

Scheme 64

the nitrothienyloxirane derivative (252d). It was thought the nitrothienyloxirane derivative (252d) may undergo acid catalysed cyclisation to the N-hydroxythienopyridinone (240d). Surprisingly the *E* and *Z* isomeric mixture of the ethyl 2-acetylprop-2-enoate derivative (236d) was recovered largely unchanged when treated with aqueous sodium hypochlorite solution in dioxane.

3.3 Studies on the Attempted Lewis Acid- catalysed Cyclisation Reactions of 2-Nitrothien-3-yloxirane Derivatives to 1,3-Dihydro-3-oxothieno[3,4-b]isoxazoles

The nitrothiophene derivatives so far investigated showed no signs of undergoing acid- catalysed cyclisation to N-hydroxythienopyridinones. Since the thiophene ring has similar aromatic character to a benzene ring investigations (Scheme 64) on ortho nitro group side- chain interactions of the *trans* nitrothienyloxirane derivative (241) were carried out using a Lewis acid as the catalyst. It was expected that the *trans* nitrothienyloxirane derivative (241) would cyclise in the presence of a lewis acid to the novel thienoisoxazole derivative (253).

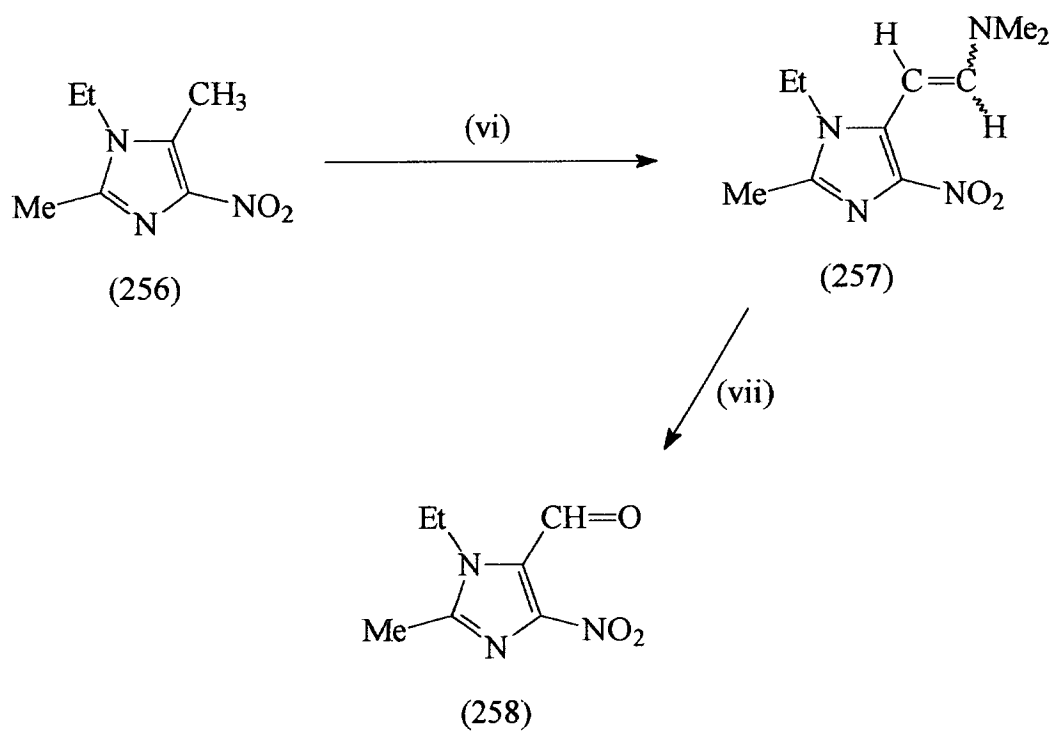
In practice the *trans* nitrothienyloxirane derivative (241) was not converted into the thienoisoxazole (253) in toluene using stannic chloride as the catalyst. Instead this reaction afforded an intractable red oil. Repeating the reaction of the nitrothienyloxirane derivative (241) with stannic chloride in dichloromethane also gave an intractable red oil. The low temperature reaction of the *trans* nitrothienyloxirane derivative (241) with stannic chloride in dichloromethane was also unsuccessful. This reaction produced only an intractable brown oil. In contrast with the low temperature reaction of the nitrothienyloxirane derivative (241) with stannic chloride, heating the *trans* nitrothienyloxirane derivative (241) under reflux with boron trifluoride etherate in dimethoxyethane gave a product in low yield (22%) which had a combustion analysis and a mass spectrum consistent with the formula $C_{13}H_9NO_4S$. This formula together with absorptions at $3400-2000\text{ cm}^{-1}$ (hydroxy group) and 1683 cm^{-1} attributed to a carbonyl group in the IR spectrum of the product allow its formulation as the acid derivative (254). The acid derivative (254) is formed by a mechanism similar to that outlined earlier (See Chapter 1, section 3.1,

page 16 and Scheme 14). The conditions of the reaction of the nitrothienyloxirane derivative (241) with boron trifluoride were modified in an attempt to make the reaction more efficient in forming the acid derivative (254). However the *trans* nitrothienyloxirane derivative (241) was recovered unchanged when its reaction with boron trifluoride was repeated at room temperature. However the acid derivative (254) was isolated in moderate yield (45%) when the *trans* nitrothienyloxirane derivative (241) was heated with boron trifluoride etherate in dimethoxyethane at 50°C. An attempt was made to prove the structure of the acid derivative (254). The acid derivative (254) was expected to react with acetic anhydride and afford the oxazine derivative (255). Disappointingly, heating the acid derivative (254) under reflux in acetic anhydride gave only an intractable oil.

3.4 CONCLUSIONS AND FUTURE WORK

It was found (Scheme 60) that 2-nitrothiophene-3-carboxaldehyde (235) condensed with active diacylmethane derivatives (136) in the presence of hydrogen chloride to give only the nitrothienylidene derivatives (236). These hydrogen chloride catalysed reactions did not afford the N-hydroxythienopyridinone derivatives (240). Future work will involve studying in greater detail the mechanism of the reaction of 2-nitrothiophene-3-carboxaldehyde (235) with a diacylmethane derivative (136) in the presence of hydrogen chloride. At present it is not understood why the nitrothienylidene derivatives (236) fail to cyclise to the thienopyridinone derivatives (240) in the presence of hydrogen chloride.

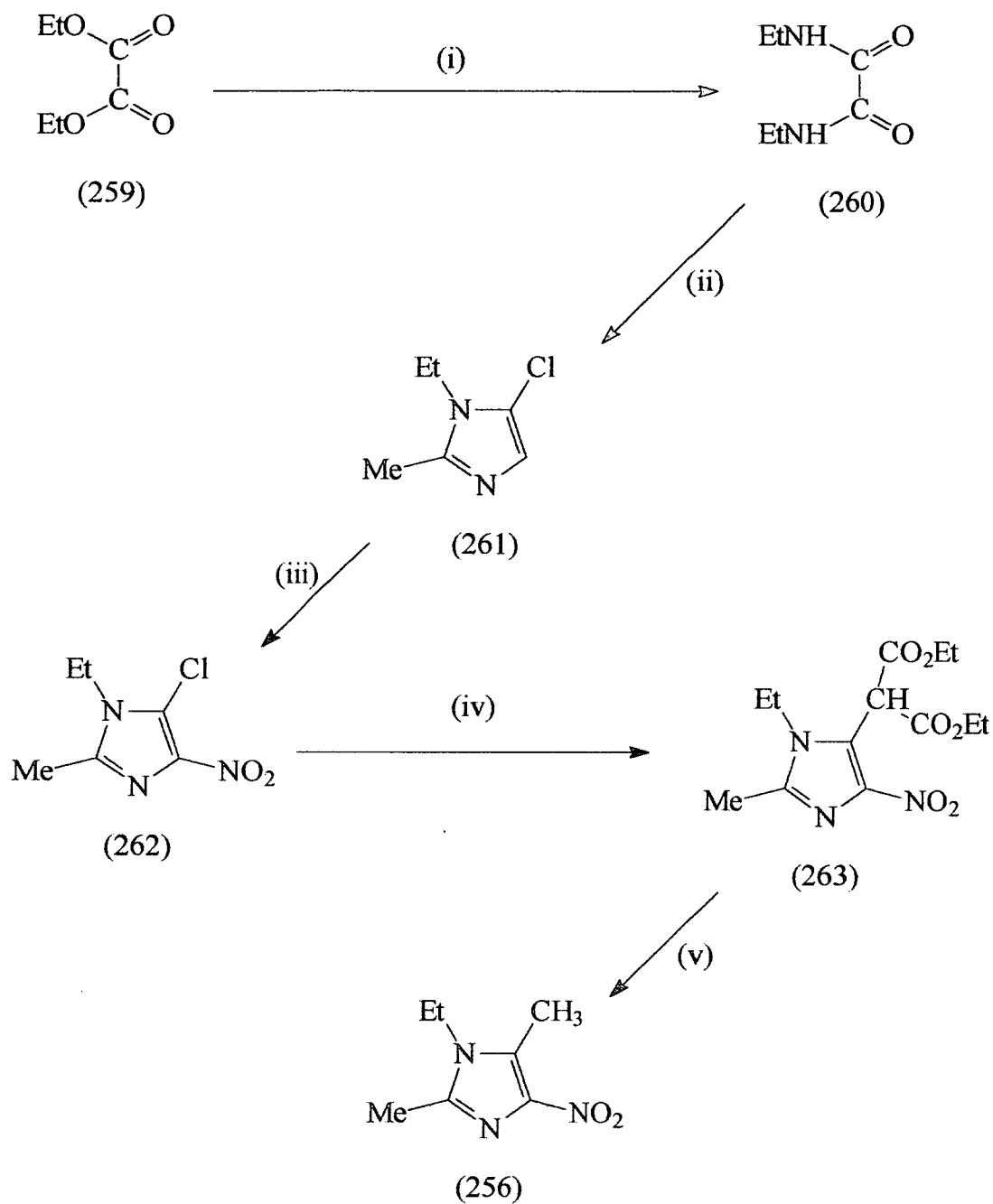
The thiophene ring (Scheme 61) in the nitrothienyloxirane derivatives (241) and (242) appeared to be exhibiting some effect with regard to their acid- catalysed cyclisation to the N-hydroxythienopyridinone derivative (243). Both the *cis* and the *trans* thienyloxirane derivatives (241) and (242) failed to react with hydrogen chloride to give the expected 1,3-dihydroxythienopyridinone derivative (243). Similarly (Scheme 63) the diacyl substituted nitrothienyloxirane derivatives (252) were not converted into the N-hydroxythienopyridinone derivatives (240). Future work will centre on synthesising other nitrothienyloxirane derivatives (252) which



(i) $\text{Me}_2\text{NCH}(\text{OMe})_2$, DMF, reflux.

(ii) NaIO_4 , THF, H_2O , room temp.

Scheme 65



(i) EtNH₂, H₂O, <15°C.

(ii) PCl₅, 100°C.

(iii) HNO₃ (conc.), H₂SO₄ (conc.), <10°C.

(iv) EtO₂CCH₂CO₂Et, NaH, DMF, 100°C.

(v) 4M HCl (aqu.), reflux.

Scheme 66

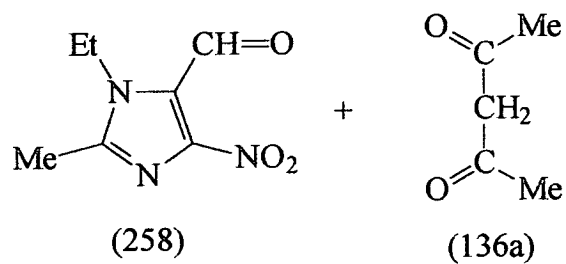
contain a *cis* acyl group in the expectation that these derivatives will react with hydrogen chloride to afford the novel N-hydroxythienopyridinone derivatives (240).

It was found (Scheme 64) that the *trans* thienyloxirane derivative (241) reacted in the presence of boron trifluoride to give the thienoic acid derivative (254) in moderate yield. This reaction is very significant since it shows that nitrothienyloxirane derivatives will undergo similar Lewis acid- catalysed reactions to those shown by nitrophenyloxirane derivatives (see Chapter 1, section 3.1, page 15, and Scheme 13). Further studies are necessary to evaluate the key factors which influence the Lewis acid promoted cyclisation reaction of the nitrothienyloxirane derivative (241) to the thenoisoxazole and related derivatives (253) and (254). Investigations will also be carried out on the Lewis acid catalysed cyclisation reaction of the *cis* thienyloxirane derivative (242) to the corresponding thenoisoxazole derivative (253).

4. STUDIES ON THE SYNTHESIS OF N-HYDROXY IMIDAZO[4,5-b]PYRIDINONES BY ACID- CATALYSED CYCLISATION REACTIONS OF ORTHO- SUBSTITUTED NITROIMIDAZOLE DERIVATIVES

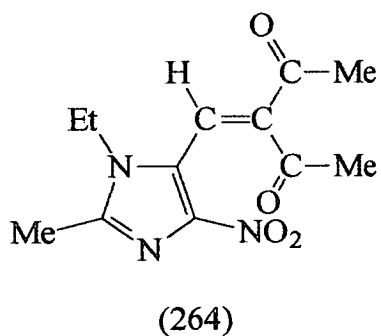
4.1 Studies on the Attempted Acid- catalysed Cyclisation Reactions of 4-Nitro-5-imidazolylidene Derivatives to 1-Hydroxy-4-imidazo[4,5-b]pyridinones

Studies under this heading were prompted by the successful syntheses and acid-catalysed cyclisation reactions of substituted nitronaphthylidene derivatives to N-hydroxybenzoquinolinone derivatives which is discussed in Chapter 3, section 2.1, page 120. The formation of N-oxygenated quinolinones by the acid- catalysed cyclisation of benzylidene derivatives is already well documented in the literature (see Chapter 1, section 3.2, page 18 and Scheme 20). The strategy again involved (Scheme 65) the initial synthesis of the 4-nitroimidazole-5-carboxaldehyde (258). In this case (Scheme 66) the 4-nitroimidazole derivative (256) was formed in five steps from diethyloxalate (259). Firstly the oxamide (260) was synthesised in good yield (79%) from the known reaction of diethyl oxalate (259) with ethylamine in water. The oxamide (260) underwent a cyclisation reaction promoted by phosphorus pentachloride at 100°C to afford the chloroimidazole derivative (261) in

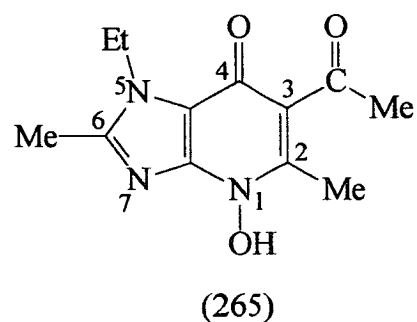


(i) or (ii)

(ii)



(iii)



(i) piperidine, AcOH, EtOH, room temp. or reflux.

(ii) $\text{HCl}_{(\text{g})}$, ether, 0°C .

(iii) $\text{HCl}_{(\text{g})}$, DME, 0°C .

Scheme 67

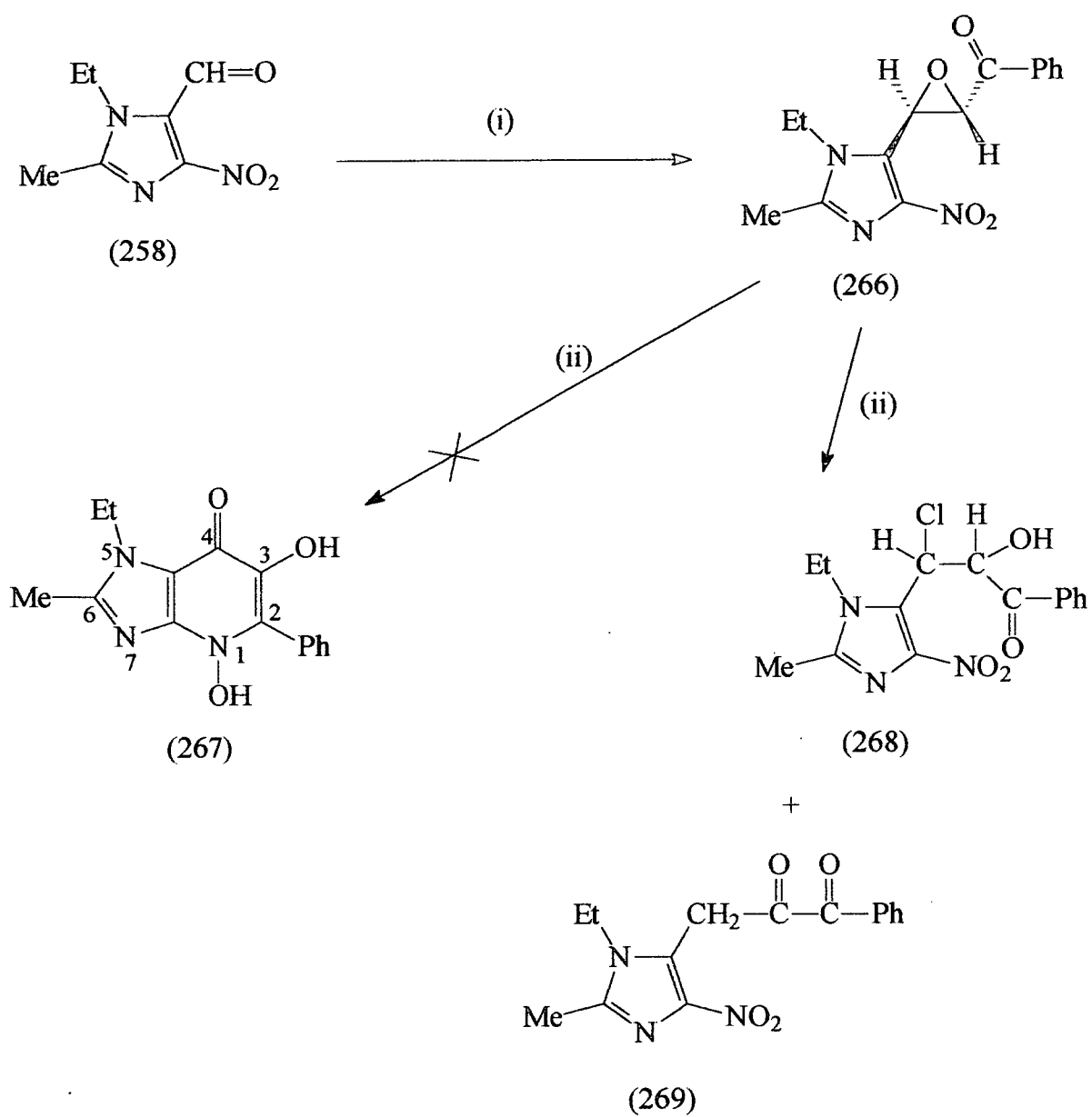
high yield. Nitration of the latter derivative (261) gave the nitroimidazole derivative (262) in good yield (71%) which was then condensed with diethyl malonate using sodium hydride in dimethylformamide at 100°C to afford the known⁹³ acetate derivative (263) in high yield. Heating the diester (263) under reflux in 4M aqueous hydrochloric acid afforded the known⁹⁴ methyl derivative (256) in good yield (78%) which had a melting point in agreement with the literature. Also the methyl derivative (256) had combustion analysis and spectroscopic data fully in accord with its assigned structure. Previous work⁸⁰ has shown how compounds similar to the nitromethyl derivative (256) could be readily transformed into the corresponding nitroaldehyde derivatives and the same method (Scheme 65) was utilised in this case. Heating the nitromethyl derivative (256) with N,N-dimethyl formamide dimethyl acetal under reflux in dimethylformamide gave a product in excellent yield whose combustion analysis and mass, IR and ¹H NMR spectra were consistent with the enamine structure (257). The enamine derivative (257) was readily converted into the imidazole-5-carboxaldehyde derivative (258) in excellent yield using sodium periodate in aqueous tetrahydrofuran. The carboxaldehyde derivative (258) was isolated as an unstable red oil which had combustion analysis and mass, IR and ¹H NMR spectra in good agreement with its structure.

Initial attempts (Scheme 67) to synthesise the novel N-hydroxyimidazopyridones (265) involved the acid-catalysed cyclisation reaction of the 4-nitroimidazole-5-carboxaldehyde derivative (258) with the active diacylmethane derivative (136a). Earlier work⁶⁶ had shown how 2-nitrobenzaldehyde derivatives condensed with active diacylmethane compounds in the presence of an acid catalyst to give the corresponding N-hydroxyquinolinones. In practice the 4-nitroimidazole-5-carboxaldehyde derivative (258) failed to react with pentan-2,4-dione (136a) in ethereal hydrogen chloride to give the N-hydroxyimidazopyridinone (265). Only unreacted starting material was recovered from this reaction.

Attention was turned to preforming the imidazolylidene derivative (264) because of the inefficiency of the acid catalysed condensation reaction of the 4-nitroimidazole-5-carboxaldehyde derivative (258) with pentane-2,4-dione (136a). The imidazolylidene derivative (264) is similar to other alkenes described earlier (see

Chapter 3, section 2.1, page 123 and Scheme 45) which are known to undergo acid-catalysed cyclisation to N-hydroxy heterocycles. Condensation of the 4-nitroimidazole-5-carboxaldehyde (258) with pentane-2,4-dione (136a) in the presence of piperidine in glacial acetic acid afforded a product in low yield (23%) whose combustion analysis and spectroscopic properties were consistent with the imidazolylidene structure (264). Also from the condensation reaction some unreacted 4-nitroimidazole-5-carboxaldehyde (258) was recovered. Further investigations were carried out on the reaction of the 4-nitroimidazole-5-carboxaldehyde (258) with pentane-2,4-dione (136a) in an attempt to improve the efficiency of the condensation between the two reactants. The imidazole-5-carboxaldehyde (258) reacted with pentane-2,4-dione (136a) in the presence of piperidine in ethanol to give only the imidazolylidene derivative (264) in low yield together with the 4-nitroimidazole-5-carboxaldehyde (258) being recovered largely unchanged. However heating the 4-nitroimidazole-5-carboxaldehyde (258) with pentane-2,4-dione (136a) in the presence of piperidine under reflux in ethanol gave the imidazolylidene derivative (264) in good yield (57%) together with some unreacted 4-nitroimidazole-5-carboxaldehyde (258). Unfortunately repeating this reaction over an extended reaction time afforded the imidazolylidene derivative (264) in moderate yield together with some unreacted 4-nitroimidazole-5-carboxaldehyde (258).

It was interesting to investigate whether this imidazolylidene derivative (264) would undergo acid-catalysed cyclisation to the corresponding N-hydroxyimidazopyridinone (265). The cyclisation reaction was rather speculative since the mechanism for this process (see Chapter 1, section 3.2, page 18 and Scheme 20) involves a step where direct entry of chloride ion is necessary into the aromatic ring. In the imidazolylidene derivative (264) there is no obvious place for the chloride ion to enter the imidazole ring. Not surprisingly the imidazolylidene derivative was recovered largely unchanged when treated with hydrogen chloride in dimethoxyethane. When this reaction was repeated over a prolonged time no N-hydroxy imidazopyridinone (265) was isolated. Disappointingly the reaction afforded only the unreacted imidazolylidene derivative (264).



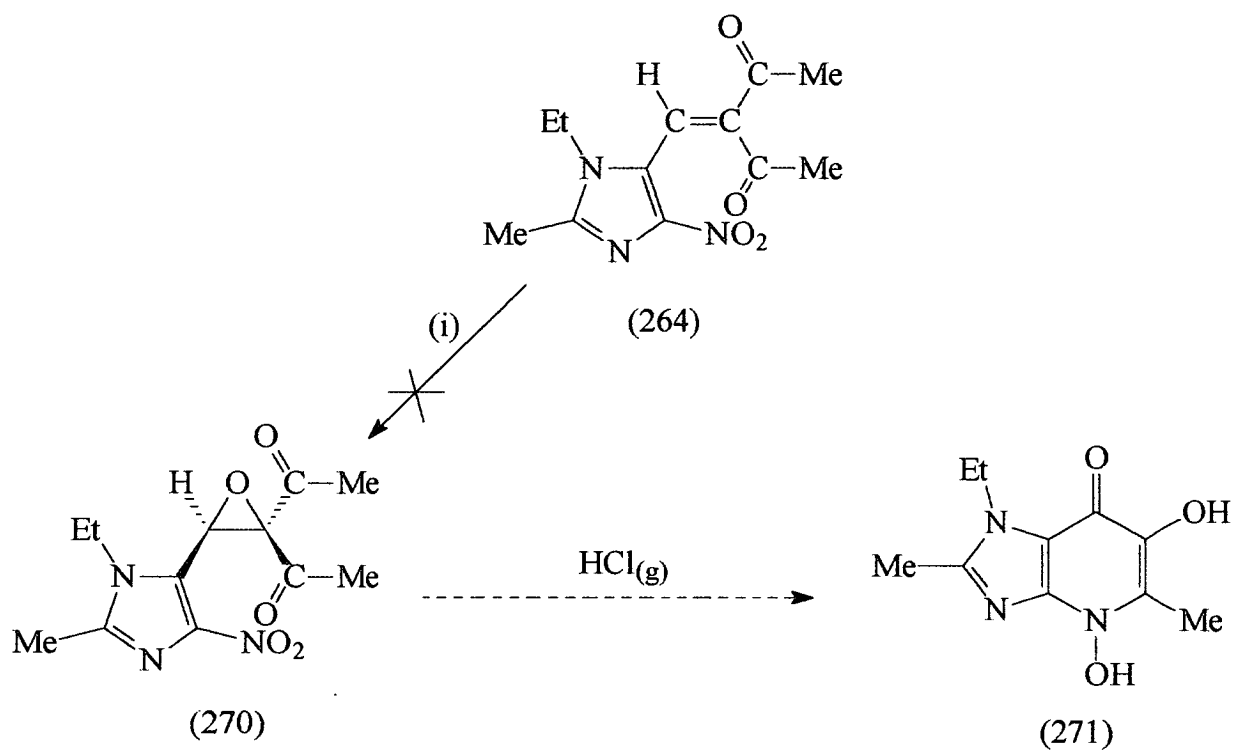
- (i) PhCOCH_2Br , NaOMe , MeOH , room temp.
(ii) $\text{HCl}_{(\text{g})}$, dioxane or DME, 11°C or 0°C .

Scheme 68

4.2 Studies on the Attempted Acid- catalysed Cyclisation Reactions of 4-Nitroimidazol-5-yloxirane Derivatives to 1,3-Dihydroxy-4-imidazo[4,5-b]pyridinones

Since the imidazolylidene derivative (264) was showing no signs of cyclising under acidic conditions to the novel N-hydroxyimidazopyridinone derivative (265) the strategy (Scheme 68) was changed to investigate the acid- catalysed cyclisation reaction of the imidazolyloxirane derivative (266) to the N-hydroxyimidazopyridinone (267). As described before this type of oxirane derivative (266) has the advantage of a built-in leaving group which makes the nucleophilic attack by the nitro group of the oxirane derivative on the electrophilic ortho side- chain occur readily (see Chapter 1, section 3.2, page 19 and Scheme 21) under acidic conditions and leads to the formation of N-oxygenated heterocycles.

Initially studies involved synthesising the *trans* imidazolyloxirane derivative (266). The *trans* imidazolyloxirane derivative (266) was obtained in high yield from the reaction of the 4-nitroimidazole-5-carboxaldehyde (258) with 2-bromoacetophenone in methanolic sodium methoxide. The *trans* imidazolyloxirane derivative (266) had combustion analysis and mass, IR and ^1H NMR spectra in good agreement with its structure. Unfortunately treating the *trans* imidazolyloxirane derivative (266) with hydrogen chloride in dioxane failed to give the N-hydroxyimidazopyridinone (267). This reaction gave only intractable oils. The *trans* imidazolyloxirane derivative (266) was recovered mostly unchanged when the reaction with hydrogen chloride was repeated in dimethoxyethane. However prolonging the reaction time of the reaction of the *trans* imidazolyloxirane derivative (266) with hydrogen chloride afforded two products. One product isolated in poor yield from the hydrogen chloride catalysed cyclisation reaction of the *trans* imidazolyloxirane derivative (266) gave a combustion analysis and showed a parent ions at m/z 340 and 338 in its mass spectrum consistent with the molecular formula $\text{C}_{15}\text{H}_{16}\text{ClN}_3\text{O}_4$. The formula together with IR absorptions at 3458 cm^{-1} (hydroxy group), and 1536 and 1349 cm^{-1} (nitro group) in the IR spectrum of the product aided its identification as the chlorohydrin derivative (268). The chlorohydrin derivative (268) also had ^1H and ^{13}C NMR spectra in accord with its structure. The second product isolated from the reaction of



(i) NaOCl (aqu.), dioxane or pyridine, room temp.

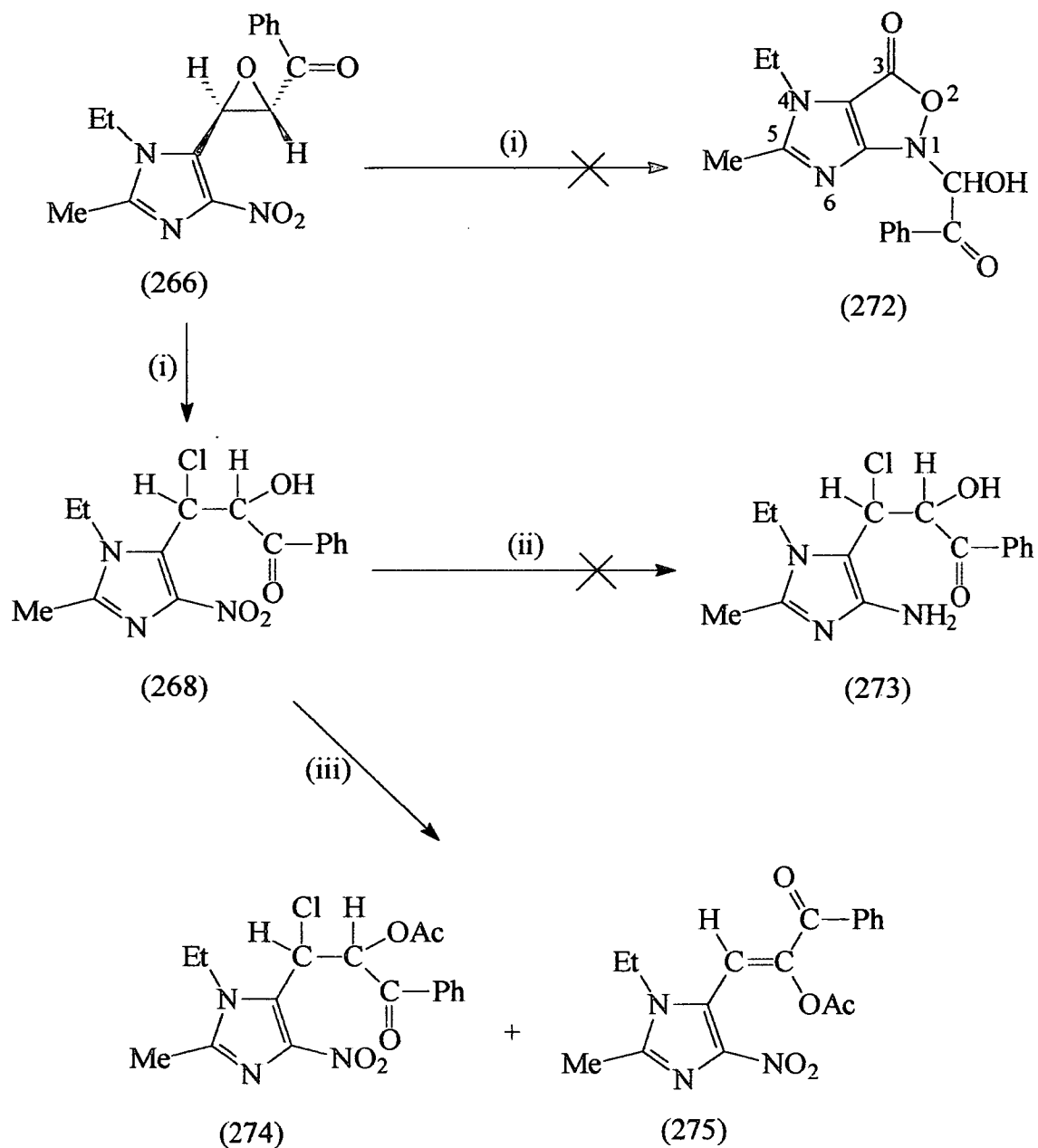
Scheme 69

the *trans* imidazolyloxirane derivative (266) with hydrogen chloride was the diketone derivative (269) in low yield whose combustion analysis and mass, IR, ^1H and ^{13}C NMR spectra were consistent with its structure.

It was obvious that the nitro group of the *trans* imidazolyloxirane derivative (266) was not interacting with the ortho side- chain when this derivative was treated with hydrogen chloride. An attempt was therefore made to synthesise an imidazolyloxirane derivative which contained a *cis* acyl group. Nitro group ortho side- chain interactions within nitrophenyloxirane derivatives are known^{68,69} to be more favourable under acidic conditions if a *cis* acyl group is present within the derivative. The strategy (Scheme 69) involved synthesising the diacyl substituted imidazolyloxirane derivative (270) from the previously formed imidazolylidene derivative (264). The diacyl substituted imidazolyloxirane derivative (270) may then undergo acid- catalysed cyclisation to the new N-hydroxyimidazopyridinone (271). Disappointingly it was found that the imidazolylidene derivative (241) reacted with aqueous sodium hypochlorite solution in dioxane to afford only an intractable oil. Similarly, an intractable oil was isolated when the reaction was repeated in pyridine instead of dioxane.

4.3 Studies on the Attempted Lewis Acid- catalysed Cyclisation Reactions of 4-Nitroimidazol-5-yloxirane Derivatives to 1,3-Dihydro-3-oxoimidazo[4,5-c]isoxazoles

Further investigations (Scheme 70) were carried out to see if the *trans* imidazolyloxirane derivative (266) would cyclise to the novel imidazoisoxazole derivative (272) using a Lewis acid. If the reaction proceeded in a similar fashion to the benzene based chemistry (see Chapter 1, section 3.1, page 16 and Scheme 14) then no chloride ion is required to enter the aromatic ring. Therefore this strategy is more feasible than using hydrogen chloride as the catalyst to aid intramolecular cyclisation of the *trans* imidazolyloxirane derivative (266) to the corresponding N-hydroxyimidazopyridinone (267).



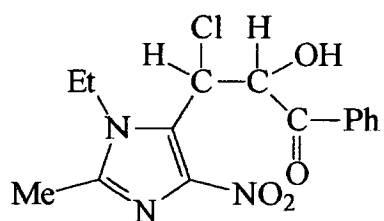
- (i) SnCl_4 , toluene or DCM, room temp.
(ii) H_2 , Pd-C, DME, room temp. and atmos. press.
(iii) Ac_2O , reflux.

Scheme 70

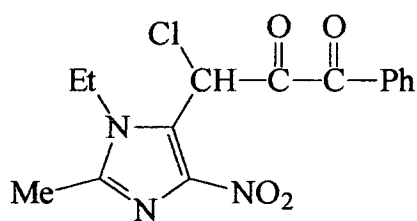
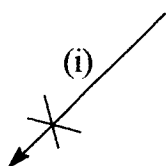
Treating the *trans* imidazolyloxirane derivative (266) with stannic chloride in toluene failed to give the imidazoisoxazole derivative (272). Instead the reaction gave the chlorohydrin derivative (268) in good yield which was identified by mp, IR and ^1H NMR spectra with a sample obtained before. The chlorohydrin derivative (268) is formed by the addition of hydrogen chloride across the oxirane ring of the *trans* imidazolyloxirane derivative (266). The hydrogen chloride required to react with the *trans* imidazolyloxirane derivative (266) must be formed on work-up of the reaction in water, where stannic chloride reacts with water to afford hydrogen chloride.

Attempts were made to prove the structure of the chlorohydrin derivative (268) by chemical methods. However heating the chlorohydrin derivative (268) under reflux in acetic anhydride afforded two products. One product isolated in low yield from the reaction gave a combustion analysis and parent ion peaks at m/z 382 and 380 in the mass spectrum in accord with the molecular formula $\text{C}_{17}\text{H}_{18}\text{ClN}_3\text{O}_5$. This molecular formula together with absorptions at 1759 and 1705 cm^{-1} (carbonyl groups) as well as nitro group absorption at 1549 and 1384 cm^{-1} in the IR spectrum of the product allow its formulation as the chlorinated ester derivative (274). The ^1H NMR spectrum of the chlorinated ester derivative (274) was in good agreement with its structure. The second product isolated in low yield from the reaction of the chlorohydrin derivative (268) with acetic anhydride showed a parent ion at m/z 343 in its mass spectrum consistent with the molecular formula $\text{C}_{17}\text{H}_{17}\text{N}_3\text{O}_5$. This formula together with IR, ^1H and ^{13}C NMR spectra allow its formulation as the imidazolylidene derivative (275). The imidazolylidene derivative (275) is thought to be formed by the loss of hydrogen chloride from the chlorinated ester derivative (274). Investigations were carried out to confirm the presence of a nitro group in the chlorohydrin derivative (268), since the IR spectrum of the chlorohydrin derivative (268) appeared to show a nitro group was present. However the chlorohydrin derivative (268) was re-isolated largely unchanged when hydrogenated in the presence of palladium-on-charcoal catalyst. None of the expected amine derivative (273) was isolated from the reaction.

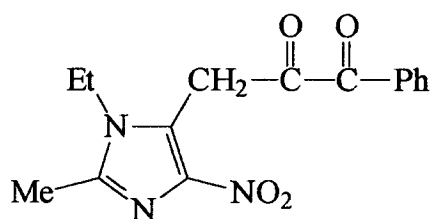
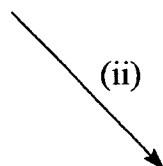
Further evidence (Scheme 71) was sought for the chlorohydrin structure (268). The IR spectrum of the chlorohydrin derivative (268) showed that a hydroxy group was



(268)



(276)

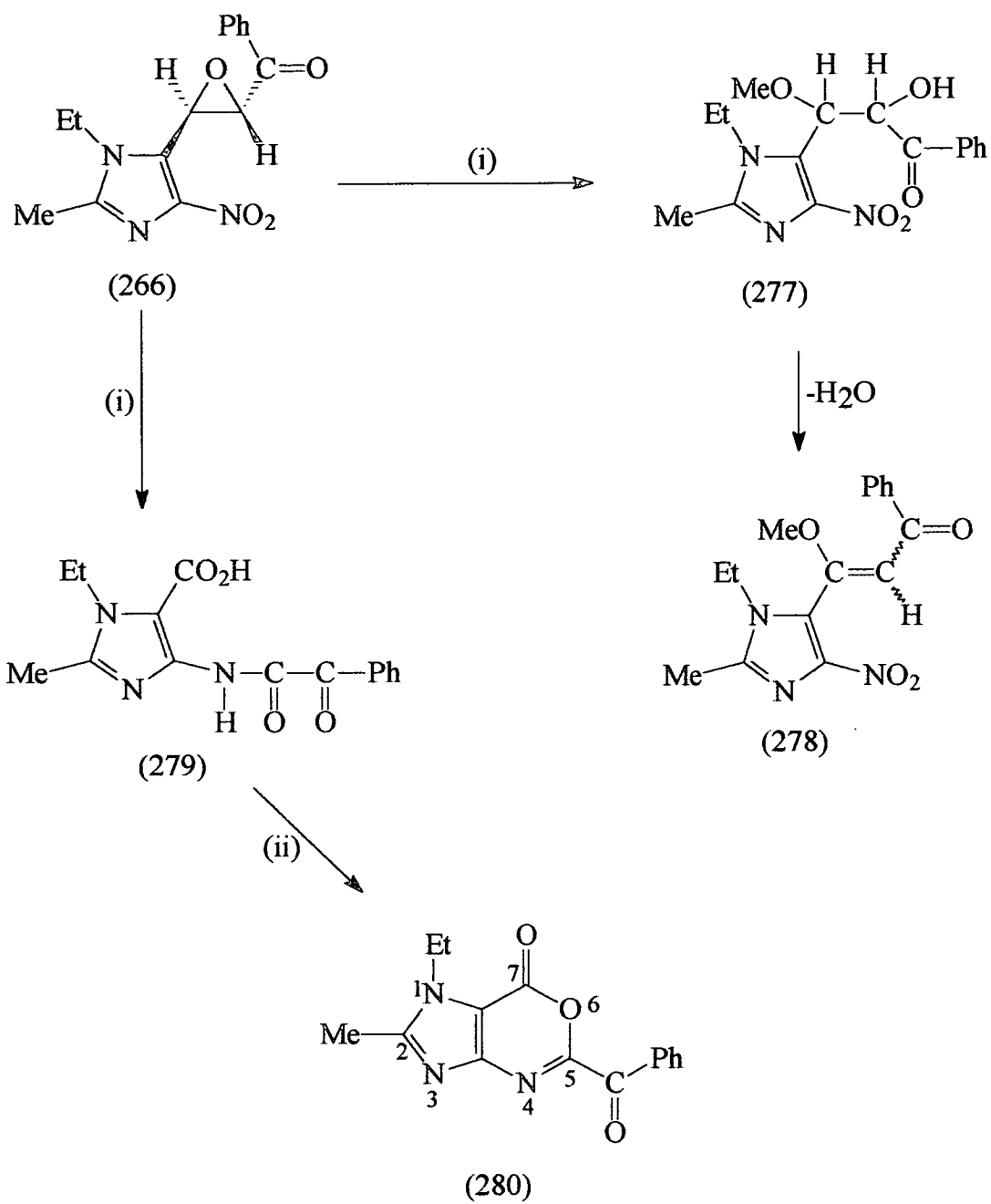


(269)

(i) MnO_2 , DME, room temp. or reflux.

(ii) $\text{BF}_3 \cdot \text{Et}_2\text{O}$, DME, reflux.

Scheme 71



(i) $\text{BF}_3 \cdot \text{Et}_2\text{O}$, DME, reflux.

(ii) Ac_2O , reflux.

Scheme 72

present in the derivative. Treating the chlorohydrin derivative (268) with manganese dioxide failed to afford the corresponding diketone derivative (276). This reaction gave only unreacted starting material. Similarly repeating the reaction of the chlorohydrin derivative (268) with manganese dioxide at elevated temperature afforded some unreacted starting material as the only identifiable material. It was also found that the chlorohydrin derivative (268) was not converted back into the imidazolyloxirane derivative (266) in the presence of sodium hydroxide, instead the reaction affording no identifiable material. However heating the chlorohydrin derivative (268) with boron trifluoride etherate under reflux in dimethoxyethane gave the diketone derivative (269) in excellent yield. The formation of the diketone derivative (269) can be accounted for by the loss of hydrogen chloride from the chlorohydrin derivative (268). Changing the solvent (Scheme 70) in the Lewis acid catalysed cyclisation reaction of the *trans* imidazolyloxirane derivative (266) failed to give the imidazopyridinone (272). It was found that the *trans* imidazolyloxirane derivative (266) was converted into the chlorohydrin derivative (268) in good yield (95%) in dichloromethane (instead of toluene) using stannic chloride as the catalyst.

Heating (Scheme 72) the *trans* imidazolyloxirane derivative (266) with boron trifluoride etherate under reflux in dimethoxyethane gave a product in moderate yield which analysed correctly and had spectroscopic properties consistent with the acid structure (279). The second product isolated in low yield from the reaction of the *trans* imidazolyloxirane derivative (266) with boron trifluoride had combustion analysis and spectroscopic properties in accord with the methoxyimidazolylidene structure (278). The acid derivative (279) is thought to be formed by an similar mechanism to that described earlier (see Chapter 1, section 3.1, page 16 and Scheme 14) whereas it is not exactly clear how the imidazolylidene derivative (278) is synthesised. The formation of the imidazolylidene derivative (278) must involve breakdown of the solvent in some way to provide the methoxy group. Nucleophilic attack by the methoxy anion on the electrophilic oxirane ring of the *trans* imidazolyloxirane derivative [(266)→(277)] causes ring opening and thus affords a hydroxy intermediate (277) subsequent dehydration of which gives the isolated product (278). An attempt was made to provide confirmatory proof of the acid derivative (279). Unfortunately heating the acid derivative (279) in acetic anhydride

under reflux gave only a product in poor yield (9%) which had a parent ion at m/z 283 in its mass spectrum together with absorption in its IR spectrum at 1743, 1696 and 1670 cm^{-1} attributed to carbonyl groups. Tentatively the product was formulated as the oxazine derivative (280).

4.4 CONCLUSIONS AND FUTURE WORK

It was found (Scheme 67) that the imidazolylidene derivative (264) failed to react with hydrogen chloride to give the corresponding N-hydroxyimidazopyridinone derivative (271). As discussed earlier with related processes (see Chapter 2, section 2, page 26, and Scheme 26) the mechanism of the reaction of benzylidene derivatives with hydrogen chloride is unclear and future studies will involve exploring the factors which influence the cyclisation process in greater detail.

It was noted (Scheme 68) that the *trans* imidazolyloxirane derivative (266) failed to undergo cyclisation to the expected 1,3-dihydroxyimidazopyridinone derivative (267) in the presence of hydrogen chloride. Future studies will investigate finding routes to *cis* imidazolyloxirane derivatives since it is hoped that these derivatives may undergo reaction with hydrogen chloride to afford novel N-hydroxyimidazopyridinone derivatives. In stark contrast (Scheme 72) to the reaction of the *trans* imidazolyloxirane derivative (266) with hydrogen chloride, the same derivative reacted with boron trifluoride to afford the imidazoic acid derivative (279). It would be interesting to compare and contrast the differing reactivities of the *trans* imidazolyloxirane derivative (266) with the corresponding *cis* imidazolyloxirane derivative with regard to their cyclisation to an imidazoisoxazole derivative in the presence of a Lewis acid. Future studies will involve finding efficient methods of synthesising *cis* imidazolyloxirane derivatives which are anticipated to cyclise to novel imidazoisoxazole derivatives promoted by a Lewis acid.

5. EXPERIMENTAL

General Experimental Details

For details of general experimental procedures see Chapter 2, section 6, page 58.

2-Methyl-1-nitronaphthalene (181)

A solution of 2-methylnaphthalene (180) (142g; 1.0mol) in glacial acetic acid (220g) was stirred and cooled to 0°C (ice- salt bath) then rapidly treated dropwise with fuming nitric acid (d=1.5)(58.0g) at such a rate that the reaction temperature remained between 0-5°C. The mixture was stirred at room temperature for 1h then at 80°C (oil bath) for 5h. The mixture was then stored in a fridge for 17h.

The resulting yellow- red suspension was filtered to afford a yellow solid which was washed with a few small portions of glacial acetic acid, combined with a second crop of solid obtained by treating the combined glacial acetic acid filtrate and washings with ice (1000g), and stirred with 1M aqueous sodium carbonate solution (500ml) for 0.5h. The resulting suspension was filtered to afford a yellow solid which was dissolved in dichloromethane and the solution dried over magnesium sulfate. Rotary evaporation of the dichloromethane solution gave a gummy yellow solid which was triturated with light petroleum to afford the nitronaphthalene derivative (181) as a yellow solid (72.0g; 39%), mp 75-77°C (Lit.,⁸¹ 80-81°C) which was identified by comparison (mp and IR spectrum) with an authentic sample.

1-(N,N-Dimethylamino)-2-(1-nitronaphth-2-yl)ethene (182)

A solution of 2-methyl-1-nitronaphthalene (181) (9.4g; 0.05mol) in anhydrous dimethylformamide (50.0ml) was mixed with a solution of N,N-dimethylformamide dimethyl acetal (11.9g; 0.1mol) in anhydrous dimethylformamide (50.0ml) and the mixture stirred and heated under reflux with the exclusion of atmospheric moisture for 18h.

The red solution was rotary evaporated under high vacuum (oil pump) to give a gummy red solid which was triturated with ether to afford the enamine (182) (12.0g; 99%), mp 99-101°C (Lit.,⁸² 98-100°C) which was used without further purification.

1-Nitro-2-naphthaldehyde (183)

(a) A solution of the enamine (182) (24.2g; 0.1mol) in tetrahydrofuran (500ml) was stirred and treated with a solution of sodium periodate (64.2g; 0.3mol) in water (500ml) added in one portion. The mixture was then stirred at room temperature for 1h.

The mixture was filtered and the inorganic filter cake washed several times with ethyl acetate allowing the washings to run into the filtrate. The filtrate was separated and the aqueous layer washed several times with ethyl acetate. The combined ethyl acetate extracts were washed with 10% w/v aqueous sodium hydrogen carbonate solution (3 x 200ml) then rotary evaporated to give the aldehyde (183) as a brown solid (19.0g; 95%), mp 97-99°C (Lit.,⁸² 99-100°C) which was used without further purification.

(b) Repetition of the reaction described in (a) before but using 1,2-dimethoxyethane as solvent and heating the reaction mixture under reflux for 4h gave the aldehyde (183) in 90% yield.

Reactions of 1-Nitro-2-naphthaldehyde (183) with Pentane-2,4-dione (136a) in the Presence of Hydrogen Chloride

(a) A solution of 1-nitro-2-naphthaldehyde (183) (2.0g; 0.01mol) in anhydrous 1,2-dimethoxyethane (45.0ml) was mixed with a solution of pentane-2,4-dione (136a) (1.0g; 0.01mol) in 1,2-dimethoxyethane (5.0ml) and the mixture was stirred and cooled to 0°C (ice- salt bath) then treated with a slow stream of hydrogen chloride until saturated. The resulting red solution was securely stoppered and stored in a fridge for 48h.

The red solution was rotary evaporated and the brown oil obtained treated with 10% w/v aqueous sodium hydrogen carbonate solution (10.0ml) and extracted several times with dichloromethane to give a viscous brown oil which was flash-chromatographed over silica, eluting with dichloromethane-ethyl acetate (1:1) to give 1-(4-chloro-1-hydroxyaminonaphth-2-yl)butane-1,3-dione (186) as a brown solid (1.0g; 36%), which formed grey microcrystals, mp 180-182°C (from ethanol), ν_{\max} 3355 (NH), 3215 br (OH), and 1706 and 1644 (C=O) cm^{-1} , $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 9.98 (1H, s, NH or OH)(exch.), 9.65 (1H, s, NH or OH)(exch.), 8.06-8.03 (1H, m, ArH), 7.92 (1H, d, J 8.0, ArH), 7.60-7.42 (2H, m, ArH), 7.40 (1H, s, ArH), 3.68 (2H, s, CH_2)(exch.), and 2.28 (3H, s, CH_3), $\delta_{\text{C}}[(\text{CD}_3)_2\text{SO}]$ 203.6 (quat.), 166.3 (quat.), 150.5 (quat.), 132.6 (quat.), 129.8 (quat.), 127.5 (CH), 124.9 (quat.), 124.5 (CH), 123.9 (CH), 123.2 (CH), 118.9 (CH), 116.3 (quat.), 51.7 (CH_2), and 30.4 (CH_3).

Found: C, 60.3; H, 4.4; N, 5.0%; m/z (FABMS), 280, 278 $[(\text{M}+\text{H})^+]$.

$\text{C}_{14}\text{H}_{12}\text{ClNO}_3$ requires: C, 60.5; H, 4.3; N, 5.0%; M, 277.5.

- (b) The reaction described in (a) before was repeated but with an extended reaction time of 96h.

The resulting suspension was rotary evaporated and the gummy brown solid obtained was treated with 10% w/v aqueous sodium hydrogen carbonate solution (20.0ml) and dichloromethane. The three phase mixture was filtered to afford the sodium salt of 1-amino-4-chloronaphthalene-2-carboxylic acid (185) which was dissolved in water (12.0ml), just acidified by the dropwise addition of glacial acetic acid and the precipitated solid collected to afford the amino acid (185) as a light brown solid (0.5g; 22%) which formed light brown microcrystals, mp 209-211°C (from ethanol- light petroleum), ν_{\max} 3494 and 3359 (NH), 3250-2000 br (OH), and 1670 (C=O) cm^{-1} , $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.45 (1H, s, NH)(exch.), 8.41 (1H, s, NH)(exch.), 8.07-7.98 (1H, m, ArH), 8.01 (1H, s, OH)(exch.), 7.82 (1H, s, ArH), 7.79-7.68 (1H, m, ArH), and 7.65-7.54 (2H, m, ArH).

Found: m/z (HREIMS), 223.0210 (M^+).

$C_{11}H_8^{37}ClNO_2$ requires: M , 223.0214.

Found: m/z (HREIMS), 221.0243 (M^+).

$C_{11}H_8^{35}ClNO_2$ requires: M , 221.0244.

The original aqueous dichloromethane filtrate was separated and the aqueous layer extracted several times with dichloromethane. Rotary evaporation of the combined dichloromethane extracts gave a dark red oil which was flash-chromatographed over silica, eluting with dichloromethane-ethyl acetate (7:3) to afford 1-(4-chloro-1-hydroxyaminonaphth-2-yl)butane-1,3-dione (186) as a light brown solid (0.4g; 14%), mp 177-180°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

Reactions of 1-Nitro-2-naphthaldehyde (183) with 1-Phenylbutane-1,3-dione (136b) in the Presence of Hydrogen Chloride

- (a) A solution of 1-nitro-2-naphthaldehyde (183) (1.0g; 0.005mol) in anhydrous 1,2-dimethoxyethane (20.0ml) was mixed with a solution of 1-phenylbutane-1,3-dione (136b) (0.81g; 0.005mol) in anhydrous 1,2-dimethoxyethane (5.0ml), 4Å molecular sieves (2.0g) were added and the mixture stirred and cooled to 0°C (ice- salt bath). The mixture was then treated with a slow stream of hydrogen chloride until saturated and the resulting red solution securely stoppered and stored in a fridge for 72h.

The mixture was filtered to remove the molecular sieves and the filtrate was rotary evaporated and the brown oil obtained treated with 10% w/v aqueous sodium hydrogen carbonate solution and extracted several times with dichloromethane. Rotary evaporation of the combined extracts gave a red- brown oil which was flash- chromatographed over silica eluting with dichloromethane to afford 1-amino-2,4-dichloronaphthalene as a brown solid (0.1g; 9%), which formed light brown microcrystals, mp 78-80°C (from light petroleum), ν_{\max} 3423, 3308 and 3217 (NH) cm^{-1} , $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.32-8.28 (1H, m, ArH), 8.06-8.01

(1H, m, ArH), 7.70-7.52 (2H, m, ArH), 7.55 (1H, s, ArH), and 6.17 (2H, s, NH₂)(exch.).

Found: C, 56.6; H, 3.4; N, 6.7%; m/z(EIMS), 215, 213, 211 (M⁺).

C₁₀H₇Cl₂N requires: C, 56.6; H, 3.3; N, 6.6%; M, 212.

The aqueous sodium hydrogen carbonate mother liquor was neutralised by the dropwise addition of glacial acetic acid and the precipitated solid collected to afford 1-amino-4-chloronaphthalene-2-carboxylic acid (185) as a light brown solid (0.14g; 15%), mp 206-209°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

- (b) The reaction described in (a) before was repeated with the omission of the molecular sieves, and with an extended reaction time of 95h.

The resulting red suspension was filtered to give the unstable hydrochloride salt of 1-amino-4-chloronaphthalene-2-carboxylic acid (185) as a light brown solid (0.79g; 71%), mp 204-206°C (decomp.), ν_{\max} 3384 br (NH), 2582-2462 br (OH), and 1692 (C=O) cm⁻¹, which was converted into 1-amino-4-chloronaphthalene-2-carboxylic acid (185) on crystallisation (from ethanol- light petroleum), mp 208-210°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

Reaction of 1-Nitro-2-naphthaldehyde (183) with 1,3-Diphenylpropane-1,3-dione (136c) in the Presence of Hydrogen Chloride

A solution of 1-nitro-2-naphthaldehyde (183) (0.40g; 0.002mol) in anhydrous ether (15.0ml) was mixed with a solution of 1,3-diphenylpropane-1,3-dione (136c) (0.45g; 0.002mol) in anhydrous ether (5.0ml) and the mixture was stirred and cooled to 0°C (ice- salt bath), then treated with a slow stream of hydrogen chloride until saturated. The resulting red solution was securely stoppered and stored in a fridge for 24h.

The resulting dark red suspension was filtered to afford the unstable hydrochloride salt of 1-amino-4-chloronaphthalene-2-carboxylic acid (185) (0.31g; 69%), mp 227-230°C, identified by comparison (IR spectrum) with a sample obtained before.

Work up of the ethereal mother liquor afforded no other identifiable material.

Reaction of 1-Nitro-2-naphthaldehyde (183) with Ethyl 3-Oxobutanoate (136d) in the Presence of Hydrogen Chloride

A solution of 1-nitro-2-naphthaldehyde (183) (1.0g; 0.005mol) in anhydrous 1,2-dimethoxyethane (20.0ml) was mixed with a solution of ethyl 3-oxobutanoate (136d) (0.65g; 0.005mol) in anhydrous 1,2-dimethoxyethane (5.0ml) and the mixture was stirred and cooled to 0°C (ice- salt bath), then treated with a slow stream of hydrogen chloride until saturated. The resulting red solution was securely stoppered and stored in a fridge for 95h.

The mixture was rotary evaporated and the semi- solid residue triturated with ethyl acetate to afford the unstable hydrochloride of 1-amino-4-chloronaphthalene-2-carboxylic acid (185) (0.52g; 47%), mp 192-195°C (decomp.), identified by comparison (mp and IR spectrum) with a sample obtained before.

Work up of the ethyl acetate mother liquor afforded no other identifiable material.

Reactions of 1-Nitro-2-naphthaldehyde (183) with Hydrogen Chloride

- (a) A solution of 1-nitro-2-naphthaldehyde (183) (4.0g; 0.02mol) in 1,2-dimethoxyethane (100ml) was cooled to 0°C (ice- salt bath) and treated with a slow stream of hydrogen chloride until saturated. The red solution was then securely stoppered and stored in a fridge for 24h.

Rotary evaporation of the red mixture gave a gummy brown solid which was triturated with ether to afford unreacted 1-nitro-2-naphthaldehyde (183) as a brown solid (3.7g; 93%), mp 94-97°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

- (b) The reaction described in (a) before was repeated with the extended reaction time of 72h.

Rotary evaporation of the mixture gave a gummy red- brown solid which was triturated with ether to afford the unstable hydrochloride of 1-amino-4-chloronaphthalene-2-carboxylic acid (185) (1.5g; 29%), mp 164-166°C, identified by comparison (IR spectrum) with a sample obtained before.

Rotary evaporation of the ethereal mother liquor afforded an oil which was flash-chromatographed in hexane-dichloromethane (1:1) over silica to afford unreacted 1-nitro-2-naphthaldehyde (183) as a mustard- yellow solid (1.5g; 38%), mp 97-99°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

6-Chloro-2-methyl-4-oxo-4H-naphth[1,2-d]-1,3-oxazine (190)

- (a) 1-Amino-4-chloronaphthalene-2-carboxylic acid (185) (0.44g; 0.002mol) was heated under reflux with acetic anhydride (5.0ml) with the exclusion of atmospheric moisture for 1h.

The resulting brown solution was rotary evaporated under high vacuum (oil pump) to give a gummy brown solid which was triturated with ether to afford 6-chloro-2-methyl-4-oxo-4H-naphth[1,2-d]-1,3-oxazine (190) as a light brown solid (0.38g; 78%), which formed brown microcrystals, mp 170-172°C (from ethanol), ν_{\max} 1748 (C=O) cm^{-1} , $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.81-8.76 (1H, m, ArH), 8.29-8.24 (1H, m, ArH), 7.99 (1H, s, ArH), 7.99-7.83 (2H, m, ArH), and 2.54 (3H, s, CH_3).

Found: C, 63.7; H, 3.3; N, 5.6%; m/z (EIMS), 247, 245 (M^+).

$\text{C}_{13}\text{H}_8\text{ClNO}_2$ requires: C, 63.5; H, 3.3; N, 5.7%; M, 245.5.

- (b) 1-Amino-4-chloronaphthalene-2-carboxylic acid (185) hydrochloride (0.51g; 0.002mol) was heated under reflux with acetic anhydride (5.0ml) for 1h then the mixture worked up as described for the reaction in (a) before to give the naphthoxazine derivative (190) as a light brown solid (0.29g; 53%), mp 166-168°C, identified by comparison (mp and IR spectrum) with a sample obtained in (a) before.

2-Acyl-3-(1-Nitronaphth-2-yl)prop-2-en-1-ones (197)

- (a) A mixture of 1-nitro-2-naphthaldehyde (183) (2.0g; 0.01mol), the corresponding 1,3-dicarbonyl compound (136) (0.012mol) and glacial acetic acid (0.8g; 0.8ml; 0.013mol) was stirred and treated at room temperature with piperidine (0.86g; 1.0ml; 0.01mol). The mixture was then stirred at room temperature with the exclusion of atmospheric moisture for 2h.

The resulting semi- solid was treated with water (10.0ml) and extracted several times with dichloromethane to give the oily product which was purified as described for the individual reactions below.

- (i) The oily product from pentane-2,4-dione (136a) was flash- chromatographed over silica, eluting with hexane-dichloromethane (1:1) to afford 3-acetyl-4-(1-nitronaphth-2-yl)but-3-en-2-one (197a) as an orange- yellow solid (28%) which formed orange- yellow microcrystals, mp 120-122°C (from ethanol), ν_{\max} 1690 (C=O), and 1593 and 1376 (NO₂) cm⁻¹, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.27 (1H, d, J 8.6, ArH), 8.18-8.13 (1H, m, ArH), 7.89-7.87(1H, m, ArH), 7.86 (1H, s, CH), 7.85-7.75 (2H, m, ArH), 7.43 (1H, d, J 8.6, ArH), 2.45 (3H, s, CH₃), and 2.20 (3H, s, CH₃).

Found: C, 67.6; H, 4.6; N, 4.9%; m/z(FABMS), 284 [(M+H)⁺].

C₁₆H₁₃NO₄ requires: C, 67.8; H, 4.6; N, 4.9%; M, 283.

- (ii) Repetition of the reaction described in (a)(i) before but with extension of the reaction time to 72h followed by the same work up afforded the alkene (197a) as a light brown solid (45%), mp 119-121°C, identified by comparison (mp and IR spectrum) with a sample obtained before.
- (iii) The oily product from 1-phenylbutane-1,3-dione (136b) was flash- chromatographed over silica eluting with hexane-dichloromethane (3:2) to afford unreacted 1-phenylbutane-1,3-dione (136b) (24%), mp 55-58°C, identified by comparison (mp and IR spectrum) with an authentic sample.

Further elution with hexane-dichloromethane (1:1) gave 3-benzoyl-4-(1-nitronaphth-2-yl)but-3-en-2-one (197b) as an orange- yellow solid (43%), which formed orange- yellow microcrystals, mp 153-155°C (from ethanol), ν_{max} 1698 (C=O), and 1591 and 1361 (NO₂) cm⁻¹, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.12-7.92 (3H, m, ArH), 7.87 (1H, s, CH), 7.83-7.29 (7H, m, ArH), 7.31 (1H, d, J 8.6, ArH), and 2.54 (3H, s, CH₃).

Found: C, 73.3; H, 4.5; N, 4.1%; m/z(APCIMS), 346 [(M+H)⁺].

C₂₁H₁₅NO₄ requires: C, 73.0; H, 4.3; N, 4.1%; M, 345.

- (iv) Repetition of the reaction described in (a)(iii) before but with extension of the reaction time to 72h followed by the same work up afforded the alkene (197b) as a light brown solid (72%), mp 150-152°C, identified by comparison (mp and IR spectrum) with a sample obtained before.
- (v) Repetition of the reaction described in (a)(iii) before but with heating at 50°C for 2h followed by the same work up afforded the alkene (197b) as a light brown solid (12%), mp 147-150°C, identified by comparison (mp and IR spectrum) with a sample obtained before.
- (vi) Repetition of the reaction described in (a)(iii) before but using dimethylformamide as solvent and with heating at 50°C for 2h followed by the same work up gave the alkene (197b) as a light brown solid (29%), mp 150-152°C, identified by comparison (mp and IR spectrum) with a sample obtained before.
- (vii) Reaction of 1-nitro-2-naphthaldehyde (183) with 1,3-diphenylpropane-1,3-dione (136c) as described in (a) before afforded a red- brown solid whose TLC in hexane-dichloromethane (1:1) over silica showed it to be only a mixture of the two starting materials (85%).
- (viii) Repetition of the reaction described in (a)(vii) before but with extension of the reaction time to 72h followed by the same work up afforded a red oil which was flash- chromatographed over silica.

Elution with hexane-dichloromethane (7:3) gave unreacted 1,3-diphenylpropane-1,3-dione (136c) as a light brown solid (37%), mp 77-79°C, identified by comparison (mp and IR spectrum) with an authentic sample.

Further elution with hexane-dichloromethane (7:3) gave a light yellow-brown solid whose TLC in hexane-dichloromethane (1:1) over silica showed it to be only a mixture of the two starting materials (46%).

Further elution with hexane-dichloromethane (1:1) gave 2-benzoyl-3-(1-nitronaphth-2-yl)-1-phenylprop-2-en-1-one (197c) as a yellow solid (17%), mp 143-145°C (from ethanol), ν_{\max} 1672 and 1642 (C=O), and 1516 and 1340 (NO₂) cm⁻¹, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.15-7.98 (5H, m, ArH), 7.97-7.80 (3H, m, ArH), 7.79-7.71 (3H, m, ArH plus CH), 7.68-7.54 (3H, m, ArH), and 7.49-7.42 (3H, m, ArH).

Found: C, 76.3; H, 4.2; N, 3.3%; m/z(EIMS), 407 (M⁺).

C₂₆H₁₇NO₄ requires: C, 76.7; H, 4.2; N, 3.4%; M, 407.

- (ix) Repetition of the reaction described in (a)(vii) before but with heating at 50°C for 72h followed by the same work up afforded a red oil which was flash-chromatographed over silica.

Elution with hexane-dichloromethane (1:1) gave an amber oil whose TLC in hexane-dichloromethane (1:1) over silica showed it to be only a mixture of the two starting materials (35%).

Further elution with hexane-dichloromethane (1:1) gave 2-benzoyl-3-(1-nitronaphth-2-yl)-1-phenylprop-2-en-1-one (197c) as a yellow-brown solid (18%), mp 141-143°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

- (x) Reaction of 1-nitro-2-naphthaldehyde (183) with ethyl 3-oxobutanoate (136d) as described in (a) before but with extension of the reaction time to 72h followed by the same work up afforded a red oil which was flash-chromatographed over silica.

Elution with hexane-dichloromethane (3:2) gave unreacted 1-nitro-2-naphthaldehyde (183) as a yellow solid (23%), mp 98-100°C, identified by comparison (mp and IR spectrum) with an authentic sample.

Further elution with hexane-dichloromethane (3:2) gave a gummy yellow solid which was triturated with ether to afford a mixture of the *E* and *Z* isomers of 2-ethoxycarbonyl-4-(1-nitronaphth-2-yl)but-3-en-2-one (197d) as a yellow solid (13%), which formed yellow microcrystals, mp 111-113°C (from ethyl acetate-light petroleum), ν_{\max} 1690 (C=O), and 1516 and 1367 (NO₂) cm⁻¹, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.31 (1H, d, J 8.7, ArH)(*Z*), 8.25 (1H, d, J 8.8, ArH)(*E*), 8.19-8.12 (2H, m, ArH)(*E* and *Z*), 7.94 (1H, s, CH)(*Z*), 7.93-7.72 (7H, m, ArH)(*E* and *Z*), 7.51 (1H, d, J 8.6, ArH)(*Z*), 7.45 (1H, d, J 8.6, ArH)(*E*), 4.29 (2H, q, J 7.1, CH₂)(*E*), 4.11 (2H, q, J 7.1, CH₂)(*Z*), 2.46 (3H, s, CH₃)(*Z*), 2.34 (3H, s, CH₃)(*E*), 1.27 (3H, t, J 7.1, CH₃)(*E*), and 0.98 (3H, t, J 7.1, CH₃)(*Z*).

Found: C, 65.5; H, 4.7; N, 4.3%; m/z (FABMS), 314 [(M+H)⁺].

C₁₇H₁₅NO₅ requires: C, 65.2; H, 4.8; N, 4.5%; M, 313.

Elution with hexane-dichloromethane (1:1) afforded the pure *Z* alkene (197d) as a yellow-brown solid (28%), which formed yellow microcrystals, mp 83-85°C (from ethyl acetate-light petroleum), ν_{\max} 1734 and 1665 (C=O), and 1526 and 1343 (NO₂) cm⁻¹, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.30 (1H, d, J 8.7, ArH), 8.18-8.13 (1H, m, ArH), 7.94 (1H, s, CH), 7.92-7.73 (3H, m, ArH), 7.51 (1H, d, J 8.6, ArH), 4.11 (2H, q, J 7.1, CH₂), 2.46 (3H, s, CH₃), and 0.98 (3H, t, J 7.1, CH₃), whose structure was verified by X-ray diffraction (see Chapter 3, section 2.1, page 126, Figure 8 and Tables 1-4).

Found: C, 65.4; H, 4.7; N, 4.4%; m/z (FABMS), 314 [(M+H)⁺].

C₁₇H₁₅NO₅ requires: C, 65.2; H, 4.8; N, 4.5%; M, 313.

- (b) A solution of 1-nitro-2-naphthaldehyde (183) (0.8g; 0.004mol) and the corresponding 1,3-dicarbonyl compound (136) (0.0048mol) in 1,2-dimethoxyethane (20.0ml) was stirred and treated at room temperature with

piperidine (0.05g) and the mixture then stirred at room temperature with the exclusion of atmospheric moisture for 2h.

The resulting red solution was rotary evaporated and the red oil obtained flash-chromatographed over silica as described for the individual reactions below.

- (i) Flash- chromatography of the red oil from pentane-2,4-dione (136a) eluting with hexane-dichloromethane (1:1) gave unreacted 1-nitro-2-naphthaldehyde (183) as a light yellow- brown solid (31%), mp 98-100°C, identified by comparison (mp and IR spectrum) with an authentic sample obtained before.

Further elution with hexane-dichloromethane (1:1) afforded 3-acetyl-4-(1-nitronaphth-2-yl)but-3-en-2-one (197a) as a yellow solid (50%), mp 119-121°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

- (ii) Repetition of the reaction described in (b)(i) before but with the addition of further pentane-2,4-dione (136a) (0.0048mol) and piperidine (0.05g) after 2h, and the resulting mixture stirred at room temperature with the exclusion of atmospheric moisture for a further 2h, gave after the same work up a red oil which was flash- chromatographed over silica.

Elution with hexane-dichloromethane (1:1) gave 3-acetyl-4-(1-nitronaphth-2-yl)but-3-en-2-one (197a) as a yellow solid (74%), mp 118-120°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

- (iii) Repetition of the reaction described in (b)(ii) before but using two molar equivalents of piperidine (0.68g; 0.8ml; 0.008mol) added in two equal aliquots, followed by the same work up gave a red oil which was flash-chromatographed over silica.

Elution with hexane-dichloromethane (1:1) gave unreacted 1-nitro-2-naphthaldehyde (183) as a yellow solid (16%), mp 98-100°C, identified by comparison (mp and IR spectrum) with an authentic sample obtained before.

Further elution with hexane-dichloromethane (1:1) gave 3-acetyl-4-(1-nitronaphth-2-yl)but-3-en-2-one (197a) as a yellow solid (32%), mp 120-122°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

- (iv) Repetition of the reaction described in (b)(i) before but using twice the previous amount of pentane-2,4-dione (136a) (0.0096mol) and piperidine (0.1g) from the outset and a total reaction time of 4h gave, after the same work up, a red oil, flash- chromatography of which over silica, eluting with hexane-dichloromethane (1:1) afforded unreacted 1-nitro-2-naphthaldehyde (183) (25%), followed by 3-acetyl-4-(1-nitronaphth-2-yl)but-3-en-2-one (197a) as a light brown solid (57%).

- (v) The oily product from 1-phenylbutane-1,3-dione (136b) was flash-chromatographed over silica.

Elution with hexane-dichloromethane (3:7) afforded a light brown solid (75%) whose TLC in hexane-dichloromethane (1:2) over silica showed it to be a mixture of the two starting materials.

Further elution with hexane-dichloromethane (3:7) afforded 3-benzoyl-4-(1-nitronaphth-2-yl)but-3-en-2-one (197b) as a yellow solid (25%), mp 150-152°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

- (vi) The oily product from 1,3-diphenylpropane-1,3-dione (136c) was flash-chromatographed over silica eluting with hexane-dichloromethane (7:3) to give unreacted 1,3-diphenylpropane-1,3-dione (136c) as a light brown solid (45%), mp 73-75°C, identified by comparison (mp and IR spectrum) with an authentic sample.

Further elution with hexane-dichloromethane (7:3) gave a light brown solid whose TLC in hexane-dichloromethane (1:2) over silica showed it to be a mixture of the two starting materials (42%), followed by unreacted 1-nitro-2-

naphthaldehyde (183) as a light brown solid (34%), mp 92-94°C, identified by comparison (mp and IR spectrum) with an authentic sample.

Elution with hexane-dichloromethane (3:2) afforded 2-benzoyl-3-(1-nitronaphth-2-yl)-1-phenylprop-2-en-1-one (197c) as a yellow solid (3%), mp 137-139°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

(vii) Repetition of the reaction described in (b)(vi) before but with an extended reaction time of 24h followed by flash- chromatography of the oily product over silica afforded by successive elution with hexane-dichloromethane (7:3) unreacted 1,3-diphenylpropane-1,3-dione (136c) (67%), a mixture of the latter with 1-nitro-2-naphthaldehyde (183) (42%), then unreacted 1-nitro-2-naphthaldehyde (183) (19%), and finally 2-benzoyl-3-(1-nitronaphth-2-yl)-1-phenylprop-2-en-1-one (197c) as a light brown solid (4%), mp 139-141°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

(viii) The oily product from ethyl 3-oxobutanoate (136d) was flash-chromatographed over silica eluting with hexane-dichloromethane (7:3) to afford *Z* 2-ethoxycarbonyl-4-(1-nitronaphth-2-yl)but-3-en-2-one (197d) as a yellow solid (12%), mp 109-111°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

Further elution with hexane-dichloromethane (7:3) gave a mixture of the *Z* and *E* isomers of 2-ethoxycarbonyl-4-(1-nitronaphth-2-yl)but-3-en-2-one (197d) as a light brown semi- solid (63%), identified by comparison [TLC in hexane-dichloromethane (1:2) over silica] with a sample obtained before.

(ix) Repetition of the reaction described in (b)(viii) before but with the addition of further ethyl 3-oxobutanoate (136d) (0.0048mol) and piperidine (0.05g) after 2h, and the resulting mixture stirred at room temperature with the exclusion of atmospheric moisture for a further 2h, gave after the same work up a red oil which was flash- chromatographed over silica, eluting with hexane-dichloromethane (3:2) to give a mixture of the *Z* and *E* isomers of 2-

ethoxycarbonyl-4-(1-nitronaphth-2-yl)but-3-en-2-one (197d) as a light brown semi- solid (73%), identified by comparison [TLC in hexane-dichloromethane (1:2) over silica] with a sample obtained before.

(x) Repetition of the reaction described in (b)(viii) before but with extension of the reaction time to 17h followed by the same work up, afforded a mixture of the *Z* and *E* isomers of 2-ethoxycarbonyl-4-(1-nitronaphth-2-yl)but-3-en-2-one (197d) as a light brown semi- solid (54%), identified by comparison (TLC in hexane-dichloromethane (1:2) over silica) with a sample obtained before.

(xi) Repetition of the reaction described in (b)(i) before but using ethanol (10.0ml) as solvent then the same work up as before afforded a red- brown semi- solid which was flash- chromatographed in hexane-dichloromethane (1:1) over silica to give unreacted 1-nitro-2-naphthaldehyde (183) as a yellow solid (46%), mp 98-100°C, identical (mp and IR spectrum) to an authentic sample prepared before, followed by 3-acetyl-4-(1-nitronaphth-2-yl)but-3-en-2-one (197a) as a yellow solid (35%), mp 118-120°C, identical (mp and IR spectrum) to a sample obtained before.

(xii) Repetition of the reaction described in (b)(xi) before but with the addition of further pentane-2,4-dione (136a) (0.0048mol) and piperidine (0.05g) after 2h, and the resulting mixture stirred at room temperature with the exclusion of atmospheric moisture for a further 2h, gave after the same work up and flash- chromatography of the resulting red- brown semi- solid in hexane-dichloromethane (1:1) over silica, unreacted 1-nitro-2-naphthaldehyde (183) (31%), followed by 3-acetyl-4-(1-nitronaphth-2-yl)but-3-en-2-one (197a) (41%), both samples of which were identified by comparison (mp and IR spectrum) with authentic samples.

Reactions of 2-Acyl-3-(1-nitronaphth-2-yl)prop-2-en-1-ones (197) with Hydrogen Chloride

A solution of the corresponding 2-acyl-3-(1-nitronaphth-2-yl)prop-2-en-1-one derivative (197) (0.012mol) in anhydrous 1,2-dimethoxyethane (120ml) was stirred and cooled to 0°C (ice- salt bath) then treated with a slow stream of hydrogen

chloride until saturated. The mixture was then securely stoppered and stored in a fridge for 24h.

The mixture was rotary evaporated and the gummy solid residue was treated with ethanol (20.0ml) and the mixture heated under reflux for 0.5h to decompose any hydrochloride salts. Rotary evaporation of the ethanolic mixture and trituration of the residue with ether or dichloromethane afforded the corresponding 3-acetyl-1,4-dihydro-1-hydroxy-2-methyl-4-oxobenzo[h]quinoline (184) which was purified as described for the individual reactions below.

- (i) 3-Acetyl-4-(1-nitronaphth-2-yl)but-3-en-2-one (197a) afforded 3-acetyl-6-chloro-1,4-dihydro-1-hydroxy-2-methyl-4-oxobenzo[h]quinoline (184a) as a pale brown solid (77%), which formed beige microcrystals, mp 204-206°C (from ethanol), ν_{\max} 3200-2000 br (OH), and 1702 and 1682 (C=O) cm^{-1} , $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 9.60 (1H, dd, J 8.1 and 0.6, ArH), 8.34 (1H, dd, J 8.3 and 1.2, ArH), 8.25 (1H, s, ArH), 7.94-7.74 (2H, m, ArH), 2.55 (3H, s, CH_3), and 2.50 (3H, s, CH_3).

Found: C, 63.7; H, 4.0; N, 4.6%; $m/z(\text{EIMS})$, 303, 301 (M^+).

$\text{C}_{16}\text{H}_{12}\text{ClNO}_3$ requires: C, 63.7; H, 4.0; N, 4.6%; M, 301.5.

Rotary evaporation of the dichloromethane mother liquor gave a gummy brown solid which was flash- chromatographed in dichloromethane-ethyl acetate (7:3) over silica to afford 1-(4-chloro-1-hydroxyaminonaphth-2-yl)butane-1,3-dione (186) as a brown solid (20%), mp 176-178°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

- (ii) Repetition of the reaction described in (i) before but with extension of the reaction time to 72h, followed by the same work up and purification afforded 3-acetyl-6-chloro-1,4-dihydro-1-hydroxy-2-methyl-4-oxobenzo[h]quinoline (184a) as a light brown solid (58%), mp 199-202°C, identified by comparison (mp and IR spectrum) with a sample obtained before, and 1-(4-chloro-1-hydroxyaminonaphth-2-yl)butane-1,3-dione (186) as a brown solid (20%), mp 177-179°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

- (iii) 3-Benzoyl-4-(1-nitronaphth-2-yl)but-3-en-2-one (197b) afforded 3-benzoyl-6-chloro-1,4-dihydro-1-hydroxy-2-methyl-4-oxobenzo[h]quinoline (184b) as a light brown solid (76%), which formed yellow microcrystals, mp 190-192°C (from ethanol), ν_{\max} 3200-2000 br (OH), and 1707 and 1606 (C=O) cm^{-1} , $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 9.58-9.53 (1H, m, ArH), 8.42-8.37 (1H, m, ArH), 8.32 (1H, s, ArH), 7.98-7.75 (2H, m, ArH), 7.51 (5H, s, ArH), and 2.33 (3H, s, CH_3).

Found: C, 69.1; H, 3.9; N, 3.8%.

$\text{C}_{21}\text{H}_{14}\text{ClNO}_3$ requires: C, 69.3; H, 3.9; N, 3.9%.

Found: m/z(HREIMS), 365.0631 (M^+).

$\text{C}_{21}\text{H}_{14}^{37}\text{ClNO}_3$ requires: M, 365.0633.

Found: m/z(HREIMS), 363.0663 (M^+).

$\text{C}_{21}\text{H}_{14}^{35}\text{ClNO}_3$ requires: M, 363.0663.

- (iv) Repetition of the reaction described in (iii) before, but with extension of the reaction time to 72h, followed by the same work up and purification afforded 3-benzoyl-6-chloro-1,4-dihydro-1-hydroxy-2-methyl-4-oxobenzo[h]quinoline (184b) as a light brown solid (88%), mp 187-189°C, identified by comparison (mp and IR spectrum) with a sample obtained before.
- (v) A mixture of the *Z* and *E* isomers of 2-ethoxycarbonyl-4-(1-nitronaphth-2-yl)but-3-en-2-one (197d) afforded ethyl 6-chloro-1,4-dihydro-1-hydroxy-2-methyl-4-oxobenzo[h]quinoline-3-carboxylate (184d) as a pale yellow solid (98%) which formed light brown microcrystals, mp 150-152°C (from light petroleum- ethanol), ν_{\max} 3600-2100 br (OH), and 1727 (C=O) cm^{-1} , $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 9.64 (1H, d, J 8.5, ArH), 8.38-8.34 (1H, m, ArH), 8.22 (1H, s, ArH), 7.96-7.74 (2H, m, ArH), 4.31 (2H, q, J 7.1, CH_2), 2.51 (3H, s, CH_3), and 1.31 (3H, t, J 7.1, CH_3).

Found: C, 60.6; H, 4.3; N, 4.2%.

C₁₇H₁₄ClNO₄ requires: C, 61.5; H, 4.2; N, 4.2%.

Found: m/z(HREIMS), 333.0578 (M⁺).

C₁₇H₁₄³⁷ClNO₄ requires: M, 333.0582.

Found: m/z(HREIMS), 331.0614 (M⁺).

C₁₇H₁₄³⁵ClNO₄ requires: M, 331.0611.

- (vi) Repetition of the reaction described in (v) before, but with extension of the reaction time to 72h, followed by the same work up and purification afforded ethyl 6-chloro-1,4-dihydro-1-hydroxy-2-methyl-4-oxobenzo[h]quinoline-3-carboxylate (184d) as a light brown solid (76%), 149-151°C, identified by comparison (mp and IR spectrum) with a sample obtained before.
- (vii) Repetition of the reaction described in (vi) before, but using *Z* 2-ethoxycarbonyl-4-(1-nitronaphth-2-yl)but-3-en-2-one (197d), followed by the same work up and purification afforded ethyl 6-chloro-1,4-dihydro-1-hydroxy-2-methyl-4-oxobenzo[h]quinoline-3-carboxylate (184d) as a light brown solid (68%), 149-151°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

1-(1-Acetoxyamino-4-chloronaphth-2-yl)butane-1,3-dione (187)

A solution of the hydroxyamino compound (186) (0.56g; 0.002mol) in anhydrous 1,4-dioxane was stirred and treated at room temperature with triethylamine (0.25g; 0.34ml; 0.002mol) added in a single portion. The mixture was then treated dropwise with a solution of acetyl chloride (0.17g; 0.0022mol) in anhydrous 1,4-dioxane (2.5ml), and stirred at room temperature with the exclusion of atmospheric moisture for 0.5h.

The light brown suspension was filtered to remove triethylamine hydrochloride and the 1,4-dioxane mother liquor was rotary evaporated under high vacuum (oil pump) and the residue treated with water (5.0ml) then extracted several times with dichloromethane to give an amber oil which was triturated with ether to afford the acetoxy derivative (187) as a light brown solid (0.35g; 55%), which formed

colourless microcrystals, mp 154-156°C (from ethyl acetate- light petroleum), ν_{\max} 3250 (NH), 1757 (N-OAc), 1722 and 1659 (C=O) cm^{-1} , $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 10.01 (1H, s, NH)(exch.), 8.23-8.19 (1H, m, ArH), 8.12-8.09 (1H, m, ArH), 7.76-7.70 (2H, m, ArH), 7.73 (1H, s, ArH), 3.72 (2H, s, CH_2)(exch.), 2.30 (3H, s, CH_3), and 2.27 (3H, s, CH_3).

Found: C, 59.8; H, 4.4; N, 4.1%; m/z (EIMS), 321, 319 (M^+).

$\text{C}_{16}\text{H}_{14}\text{ClNO}_4$ requires: C, 60.1; H, 4.4; N, 4.4%; M, 319.5.

1-(4-Chloro-1-hydroxyaminonaphth-2-yl)butane-1,3-dione Oxime (188)

A solution of the diketone (186) (0.56g; 0.002mol) in anhydrous ethanol (10.0ml) was stirred and treated with a solution of hydroxylamine hydrochloride (0.7g; 0.01mol) in anhydrous ethanol (25.0ml) added in one portion, followed by a single portion of anhydrous sodium carbonate (0.53g; 0.005mol). The resulting suspension was then stirred at room temperature with the exclusion of atmospheric moisture for 24h.

The resulting light brown suspension was rotary evaporated and the residue was treated with water (5.0ml) then extracted several times with dichloromethane to give a gummy brown solid (0.5g) which was flash- chromatographed over silica.

Elution with dichloromethane gave the oxime derivative (188) as a light brown solid (0.18g; 31%) which formed pale grey microcrystals, mp 128-130°C (from ethanol), ν_{\max} 3304 br (NH and OH), and 1627 (C=O) cm^{-1} , $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 10.61 (1H, s, NH or OH)(exch.), 9.96 (1H, br s, NH or OH)(exch.), 9.63 (1H, s, NH or OH)(exch.), 8.07-8.03 (1H, m, ArH), 7.81-7.77 (1H, m, ArH), 7.60-7.42 (2H, m, ArH), 7.40 (1H, s, ArH), 3.35 (2H, s, CH_2), and 1.89 (3H, s, CH_3).

Found: C, 57.1; H, 4.5; N, 9.3%.

C₁₄H₁₃ClN₂O₃ requires: C, 57.4; H, 4.4; N, 9.6%.

Found: m/z(HREIMS), 294.0588 (M⁺).

C₁₄H₁₃³⁷ClN₂O₃ requires: M, 294.0585.

Found: m/z(HREIMS), 292.0618 (M⁺).

C₁₄H₁₃³⁵ClN₂O₃ requires: M, 292.0615.

The Attempted Oxidation of 1-(4-Chloro-1-hydroxyaminonaphth-2-yl)butane-1,3-dione (186) Using Manganese Dioxide in 1,2-Dimethoxyethane

A solution of the hydroxyamino compound (186) (0.56g; 0.002mol) in anhydrous 1,2-dimethoxyethane (10.0ml) was stirred and treated at room temperature with activated manganese dioxide (Aldrich, 21,764-6)(1.0g), added in one portion. The resulting suspension was then stirred at room temperature with the exclusion of atmospheric moisture for 0.5h.

The suspension was filtered through Celite and the pad was washed several times with anhydrous 1,2-dimethoxyethane. Rotary evaporation of the 1,2-dimethoxyethane filtrate and washings gave a dark red- brown oil (0.5g) which yielded no identifiable material.

1-Acetoxy-3-acyl-1,4-dihydro-2-methyl-4-oxobenzo[h]quinolines (198)

A solution of the corresponding 3-acyl-1,4-dihydro-1-hydroxy-2-methyl-4-oxobenzo[h]quinoline (184) (0.004mol) in anhydrous 1,4-dioxane (15.0ml) was stirred and treated at room temperature with triethylamine (0.5g; 0.68g; 0.004mol) added in a single portion. The mixture was then treated dropwise with a solution of acetyl chloride (0.34g; 0.0044mol) in anhydrous 1,4-dioxane (5.0ml), and stirred at room temperature with the exclusion of atmospheric moisture for 0.5h.

The mixture was filtered to remove triethylamine hydrochloride and the filtrate was rotary evaporated. The residue was treated with water (10.0ml) and extracted several times with dichloromethane to give a gummy solid which was triturated with ether to afford the corresponding 1-acetoxy-3-acyl-1,4-dihydro-2-methyl-4-

oxobenzo[h]quinoline derivative (198) as described for the individual reactions below.

- (i) 3-Acetyl-1,4-dihydro-1-hydroxy-2-methyl-4-oxobenzo[h]quinoline (184a) afforded the acetoxy derivative (198a) as a light brown solid (64%), which formed beige microcrystals, mp 123-125°C (from ethyl acetate), ν_{\max} 1800 (N-OAc), and 1693 (C=O) cm^{-1} , $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.86-8.82 (1H, m, ArH), 8.36-8.31 (1H, m, ArH), 8.17 (1H, s, ArH), 7.94-7.80 (2H, m, ArH), 2.56 (3H, s, CH₃), 2.39 (3H, s, CH₃).

Found: C, 63.3; H, 4.1; N, 4.0%.

C₁₈H₁₄ClNO₄ requires: C, 62.9; H, 4.1; N, 4.1%.

Found: m/z(HREIMS), 345.0576 (M⁺).

C₁₈H₁₄³⁷ClNO₄ requires: M, 345.0582.

Found: m/z(HREIMS), 343.0613 (M⁺).

C₁₈H₁₄³⁵ClNO₄ requires: M, 343.0611.

- (ii) 3-Benzoyl-1,4-dihydro-1-hydroxy-2-methyl-4-oxobenzo[h]quinoline (184b) afforded the acetoxy derivative (198b) as a light brown solid (74%), which formed beige microcrystals, mp 114-116°C (from ethyl acetate), ν_{\max} 1806 (N-OAc), and 1691 (C=O) cm^{-1} , $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.87 (1H, d, J 8.5, ArH), 8.37 (1H, d, J 8.0, ArH), 8.26 (1H, s, ArH), 7.99-7.81 (2H, m, ArH), 7.57 (5H, br s, ArH), 2.39 (3H, s, CH₃), and 1.85 (3H, s, CH₃).

Found: C, 68.3; H, 4.0; N, 3.4%; m/z(EIMS), 407, 405 (M⁺).

C₂₃H₁₆ClNO₄ requires: C, 68.1; H, 3.9; N, 3.5%; M, 405.5.

- (iii) 1,4-Dihydro-3-ethoxycarbonyl-1-hydroxy-2-methyl-4-oxobenzo[h]quinoline (184d) afforded the acetoxy derivative (198d) as a light brown solid (67%), which formed beige microcrystals, mp 138-140°C (from dimethylformamide-ethyl acetate), ν_{\max} 1814 (N-OAc), and 1730 (C=O) cm^{-1} , $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.91-8.86 (1H, m, ArH), 8.40-8.35 (1H, m, ArH), 8.17 (1H, s, ArH), 8.00-7.83 (2H,

m, ArH), 4.34 (2H, q, J 7.1, CH₂), 2.51 (3H, s, CH₃), 2.43 (3H, s, CH₃), and 1.31 (3H, t, J 7.1, CH₃).

Found: C, 60.9; H, 4.9; N, 4.2%.

C₁₉H₁₆ClNO₅ requires: C, 61.0; H, 4.3; N, 3.7%.

Found: m/z(HREIMS), 375.0690 (M⁺).

C₁₉H₁₆³⁷ClNO₅ requires: M, 375.0688.

Found: m/z(HREIMS), 373.0720 (M⁺).

C₁₉H₁₆³⁵ClNO₅ requires: M, 373.0717.

3-Acyl-1,4-dihydro-2-methyl-4-oxobenzo[h]quinolines (199)

An equivalent weight of sodium dithionite was added to a solution of the corresponding 3-acyl-1,4-dihydro-1-hydroxy-2-methyl-4-oxobenzo[h]quinoline derivative (184) (0.002mol) in 70% v/v aqueous ethanol (40.0ml) and the mixture was stirred and heated under reflux for 0.5h. A second equivalent weight of sodium dithionite was then added and stirring and heating under reflux continued for a further 0.5h.

The resulting yellow suspension was rotary evaporated and the residue treated with water (5.0ml) and filtered to afford the corresponding 3-acyl-1,4-dihydro-2-methyl-4-oxobenzo[h]quinoline derivative (199) which was purified as described for the individual reactions below.

- (i) 3-Acetyl-1,4-dihydro-1-hydroxy-2-methyl-4-oxobenzo[h]quinoline (184a) afforded 3-acetyl-1,4-dihydro-2-methyl-4-oxobenzo[h]quinoline (199a) as a light brown solid (84%) which formed beige microcrystals, mp 240-242°C (from ethanol), ν_{\max} 3344 and 3268 (NH), and 1681 (C=O) cm⁻¹, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 11.59 (1H, br s, NH), 9.02-8.98 (1H, m, ArH), 8.30-8.25 (1H, m, ArH), 8.15 (1H, s, ArH), 7.94-7.83 (2H, m, ArH), 2.56 (3H, s, CH₃), and 2.54 (3H, s, CH₃).

Found: C, 67.1; H, 4.3; N, 4.7%; m/z(EIMS), 287, 285 (M⁺).

C₁₆H₁₂ClNO₂ requires: C, 67.3; H, 4.2; N, 4.9%; M, 285.5.

- (ii) 3-Benzoyl-1,4-dihydro-1-hydroxy-2-methyl-4-oxobenzo[h]quinoline (184b) afforded 3-benzoyl-1,4-dihydro-2-methyl-4-oxobenzo[h]quinoline (199b) as a light brown solid (92%) which formed beige microcrystals, mp 230-232°C (from ethanol), ν_{\max} 3476, 3341 and 3227 (NH), and 1682 (C=O) cm^{-1} , $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 9.07 (1H, d, J 8.1, ArH), 8.26 (1H, d, J 8.1, ArH), 8.20 (1H, s, ArH), 7.92-7.75 (2H, m, ArH), 7.62-7.52 (5H, m, ArH), and 2.42 (3H, s, CH_3).

Found: $m/z(\text{HREIMS})$, 349.0678 (M^+).

$\text{C}_{21}\text{H}_{14}^{37}\text{ClNO}_2$ requires: M, 349.0684.

Found: $m/z(\text{HREIMS})$, 347.0701 (M^+).

$\text{C}_{21}\text{H}_{14}^{35}\text{ClNO}_2$ requires: M, 347.0713.

- (iii) 1,4-Dihydro-3-ethoxycarbonyl-1-hydroxy-2-methyl-4-oxobenzo[h]quinoline (184d) afforded 1,4-dihydro-3-ethoxycarbonyl-2-methyl-4-oxobenzo[h]quinoline (199d) as a light brown solid (94%) which formed beige microcrystals, mp 195-197°C (from ethanol- acetic acid), ν_{\max} 3372 and 3248 (NH), and 1697 and 1636 (C=O) cm^{-1} , $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 11.51 (1H, br s, NH)(exch.), 8.92-8.88 (1H, m, ArH), 8.22-8.17 (1H, m, ArH), 8.05 (1H, s, ArH), 7.89-7.77 (2H, m, ArH), 4.28 (2H, q, J 7.1, CH_2), 2.52 (3H, s, CH_3), and 1.28 (3H, t, J 7.1, CH_3).

Found: C, 64.4; H, 4.5; N, 4.4%; $m/z(\text{EIMS})$, 317, 315 (M^+).

$\text{C}_{17}\text{H}_{14}\text{ClNO}_3$ requires: C, 64.7; H, 4.4; N, 4.4%; M, 315.5.

Trans 2-Benzoyl-3-(1-nitronaphth-2-yl)oxirane (202)

A suspension of 1-nitro-2-naphthaldehyde (183) (8.0g; 0.04mol) and 2-bromoacetophenone (8.0g; 0.04mol) in methanol (120.0ml) was stirred and cooled to 0-10°C (ice bath) then treated dropwise with a solution of sodium (0.92g; 0.04g atom) in methanol (40.0ml). The mixture was then stirred at room temperature with the exclusion of atmospheric moisture for 3h.

The suspension was acidified to pH 6 by the addition of glacial acetic acid and then filtered to afford the oxirane derivative (202) as a light brown solid (11.4g; 89%) which formed light brown microcrystals, mp 163-165°C (from ethyl acetate), ν_{\max} 1701 (C=O), and 1522 and 1377 (NO₂) cm⁻¹, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.35 (1H, d, J 8.7, ArH), 8.21-8.16 (1H, m, ArH), 8.12-8.06 (2H, m, ArH), 7.91-7.54 (7H, m, ArH), 4.95 (1H, d, J 2.0, CH), and 4.38 (1H, d, J 2.0, CH).

Found: C, 70.9; H, 4.3; N, 4.4%; m/z (HREIMS), 319.0852 (M⁺).

C₁₉H₁₃NO₄ requires: C, 71.5; H, 4.1; N, 4.4%; M, 319.0845.

Reactions of *Trans* 2-Benzoyl-3-(1-nitronaphth-2-yl)oxirane (202) with Hydrogen Chloride

(a) A solution of *trans* 2-benzoyl-3-(1-nitronaphth-2-yl)oxirane (202) (1.3g; 0.004mol) in anhydrous 1,4-dioxane (50.0ml) was stirred and cooled to 11°C (ice- salt bath) then treated with a slow stream of hydrogen chloride until saturated. The mixture was then securely stoppered and stored in a fridge for 24h.

The red solution was rotary evaporated to give a red oil which was treated with 10% w/v aqueous sodium hydrogen carbonate solution (5.0ml) and extracted several times with dichloromethane. Rotary evaporation of the dichloromethane extract gave a red oil (1.1g) which was flash- chromatographed over silica.

Elution with hexane-dichloromethane (2:3) gave 3-chloro-3-(1-nitronaphth-2-yl)-1-phenylprop-2-en-1-one (203) as an orange solid (0.52g; 39%), which formed orange microcrystals, mp 151-153°C (from ethyl acetate), ν_{\max} 1657 (C=O), and 1526 and 1373 (NO₂) cm⁻¹, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.52-7.80 (5H, m, ArH), and 7.77-7.50 (7H, m, ArH plus CH), $\delta_{\text{C}}[(\text{CD}_3)_2\text{SO}]$ complex mixture.

Found: C, 67.9; H, 3.3; N, 4.2%; m/z (FABMS), 340, 338 [(M+H)⁺].

C₁₉H₁₂ClNO₃ requires: C, 67.6; H, 3.6; N, 4.1%; M, 337.5.

(b) A solution of *trans* 2-benzoyl-3-(1-nitronaphth-2-yl)oxirane (202) (3.2g; 0.01mol) in anhydrous 1,2-dimethoxyethane (100.0ml) was stirred and cooled to

0°C (ice- salt bath) then treated with a slow stream of hydrogen chloride until saturated. The mixture was then securely stoppered and stored in a fridge for 24h.

The red solution was rotary evaporated to give a red oil which was treated with 10% w/v aqueous sodium hydrogen carbonate solution (10.0ml) and then extracted several times with dichloromethane. Rotary evaporation of the dichloromethane extract gave a red oil (2.7g) which was flash- chromatographed over silica.

Elution with hexane-dichloromethane (1:1) gave impure 3-chloro-3-(1-nitronaphth-2-yl)-1-phenylprop-2-en-1-one (203) (0.93g; 28%) as a yellow solid, mp 136-139°C, identified by comparison [mp, IR spectrum and TLC in hexane-dichloromethane (1:2) over silica] with a sample obtained before.

- (c) Repetition of the reaction described in (b) before but with extension of the reaction time to 72h followed by the same work up gave a dark red oil (3.3g) which was flash- chromatographed over silica.

Elution with hexane-dichloromethane (1:1) gave impure 3-chloro-3-(1-nitronaphth-2-yl)-1-phenylprop-2-en-1-one (203) as a yellow solid (1.0g; 30%), mp 142-145°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

Elution with hexane-dichloromethane (1:1) gave an amber coloured oil (0.4g) which was triturated with ether to afford 1-benzoyl-2-chloro-1-hydroxy-2-(1-nitronaphth-2-yl)ethane (205) as a yellow solid (0.21g; 6%) which formed yellow microcrystals, mp 138-140°C (from light petroleum- ethyl acetate), ν_{\max} 3575 (OH), 1667 (C=O), and 1527 and 1353 (NO₂) cm⁻¹, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.47-8.06 (5H, m, ArH), 7.79-7.59 (6H, m, ArH), 6.82 (1H, d, J 5.3, OH)(exch.), 5.87 (1H, d, J 9.6, CH), and 5.35-5.29 (1H, m, CH).

Found: C, 65.0; H, 3.5; N, 3.9%.

C₁₉H₁₄ClNO₄ requires: C, 64.1; H, 3.9; N, 3.9%.

Found: M/z(FABMS), 358.0662 [(M+H)⁺].

C₁₉H₁₄³⁷ClNO₄ requires: (M+H), 358.0660.

Found: M/z(FABMS), 356.0685 [(M+H)⁺].

C₁₉H₁₄³⁵ClNO₄ requires: (M+H), 356.0690.

Further elution with hexane-dichloromethane (1:1) gave an amber coloured oil (0.6g) which was triturated with ether to afford 5-chloro-1,3-dihydro-3-(1-hydroxy-2-oxo-2-phenyl)ethylnaphth[1,2-c]isoxazole (204) as a yellow solid (0.42g; 12%) which formed pale yellow microcrystals, mp 124-126°C (from light petroleum- ethyl acetate), ν_{\max} 3457 (OH), and 1685 (C=O) cm⁻¹, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.42-8.38 (1H, m, ArH), 8.17-8.04 (3H, m, ArH), 7.95 (1H, s, ArH), 7.89-7.75 (2H, m, ArH), 7.72-7.52 (2H, m, ArH), 7.36 (1H, s, ArH), 7.05 (1H, br s, OH)(exch.), and 6.96 (1H, s, CH), $\delta_{\text{C}}[(\text{CD}_3)_2\text{SO}]$ 195.2 (quat.), 164.8 (quat.), 154.6 (quat.), 134.3 (2 x quat.), 134.1 (CH), 131.2 (CH), 130.4 (quat.), 129.5 (CH), 129.0 (4 x CH), 125.7 (CH), 124.0 (CH), 121.8 (quat.), 117.2 (CH), 113.0 (quat.), and 69.1 (CH).

Found: C, 67.7; H, 3.5; N, 4.0%; m/z(EIMS), 339, 337 (M⁺).

C₁₉H₁₂ClNO₃ requires: C, 67.6; H, 3.6; N, 4.1%; M, 337.5.

The Attempted Catalytic Reduction of 3-Chloro-3-(1-nitronaphth-2-yl)-1-phenylprop-2-en-1-one (203)

3-Chloro-3-(1-nitronaphth-2-yl)-1-phenylprop-2-en-1-one (203) (0.34g; 0.001mol) was hydrogenated in ethanol (20.0ml) over palladium-on-charcoal (0.03g) at room temperature and atmospheric pressure until no further hydrogen was absorbed.

The mixture was filtered through Celite and the pad washed several times with small portions of ethanol. Rotary evaporation of the combined ethanol filtrate and washings gave a viscous red oil (0.2g), flash- chromatography of which yielded no identifiable material.

Attempted Oxidation Reactions of 3-Chloro-3-(1-nitronaphth-2-yl)-1-phenylprop-2-en-1-one (203)

- (a) A solution of 3-chloro-3-(1-nitronaphth-2-yl)-1-phenylprop-2-en-1-one (203) (0.34g; 0.001mol) in 70% v/v aqueous glacial acetic acid (15.0ml) was stirred and treated at room temperature with solid chromium trioxide (0.68g) brushed into the solution in small portions. The mixture was then stirred and heated at 100°C for 0.5h.

The dark red solution was rotary evaporated under high vacuum (oil pump) and the dark brown residue was treated with water (5.0ml) then extracted several times with dichloromethane to give impure benzoic acid as a light brown solid (0.13g; 100%), mp 101-103°C, identified by comparison (mp and IR spectrum) with an authentic sample.

- (b) A solution of 3-chloro-3-(1-nitronaphth-2-yl)-1-phenylprop-2-en-1-one (203) (0.34g; 0.001mol) in anhydrous tetrahydrofuran (10.0ml) was stirred and treated at room temperature with activated manganese dioxide (Aldrich 21,764-6)(0.5g) added in one portion. The mixture was then stirred at room temperature for 2.75h.

The mixture was filtered through Celite and the pad washed several times with small portions of anhydrous tetrahydrofuran. Rotary evaporation of the combined tetrahydrofuran filtrate and washings gave a gummy solid (0.4g) which was triturated with ether to afford impure starting material (203) (0.26g; 76%), mp 140-144°C, identified by comparison [mp, IR spectrum and TLC in hexane-dichloromethane (1:2) over silica] with a sample obtained before.

Attempted Reduction Reactions of 5-Chloro-1,3-dihydro-3-(1-hydroxy-2-oxo-2-phenyl)ethylnaphth[1,2-c]isoxazole (204)

- (a) The naphthisoxazole derivative (204) (0.068g; 0.0002mol) was hydrogenated in ethanol (20.0ml) over palladium-on-charcoal (0.007g) at room temperature and atmospheric pressure until no further hydrogen was absorbed.

The mixture was filtered through Celite and the pad washed several times with small portions of ethanol. Rotary evaporation of the combined ethanol filtrate and washings gave an intractable viscous red- brown oil (0.06g) whose TLC in hexane-dichloromethane (1:2) over silica showed it to be a multicomponent mixture which was not further investigated.

- (b) An equivalent weight of sodium dithionite was added to a solution of the naphthisoazole derivative (204) (0.1g; 0.0003mol) in 70% v/v aqueous ethanol (5.0ml) and the mixture was stirred and heated under reflux for 0.5h. A second equivalent weight of sodium dithionite was then added and stirring and heating under reflux continued for a further 0.5h.

The resulting yellow suspension was rotary evaporated and the residue treated with water (1.0ml) and filtered to afford unreacted starting material (204) as a light brown solid (0.07g; 70%), mp 122-124°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

The Attempted Base- catalysed Epimerisation of *Trans* 2-Benzoyl-3-(1-nitronaphth-2-yl)oxirane (202)

A suspension of the *trans* oxirane (202) (0.64g; 0.002mol) in methanol (20.0ml) was stirred and treated at room temperature with a solution of sodium methoxide in methanol [0.4ml of a 10% solution of sodium (0.5g) in methanol (4.5ml)]. The mixture was then stirred at room temperature with the exclusion of atmospheric moisture for 18h.

The suspension was made acidic by the dropwise addition of glacial acetic acid then filtered to afford the unreacted *trans* oxirane (202) (0.62g; 97%), mp 161-163°C, which was identified by comparison (mp, and IR and ¹H NMR spectra) with a sample obtained before.

The Reaction of 3-Benzoyl-4-(1-nitronaphth-2-yl)but-3-en-2-one (197b) with Aqueous Sodium Hypochlorite

A solution of the alkene (197b) (1.7g; 0.005mol) in 1,4-dioxane (25.0ml) was stirred and treated at room temperature with aqueous sodium hypochlorite solution (14-15%

available chlorine; ca.2M)(12.5ml; 0.025mol). The mixture was then stirred at room temperature for 10min.

The yellow solution was rotary evaporated at as low a temperature as possible and the residue was treated with water (10.0ml) then extracted several times with dichloromethane to give a brown solid (1.0g) which was flash- chromatographed over silica.

Elution with hexane-ether (4:1) gave a gummy brown solid (0.12g) which was triturated with ether to afford *cis* 2-Benzoyl-3-(1-nitronaphth-2-yl)oxirane (212) as a light brown solid (0.05g; 3%) which formed beige microcrystals, mp 135-137°C (from ethanol), ν_{\max} 1684 (C=O), and 1516 and 1354 (NO₂) cm⁻¹.

Found: C, 71.4; H, 4.0; N, 4.3%; m/z(FABMS), 320 [(M+H)⁺].

C₁₉H₁₃NO₄ requires: C, 71.5; H, 4.1; N, 4.4%; M, 319.

Further elution with hexane-ether (4:1) gave a brown solid (0.1g) whose TLC in hexane-ether (1:1) over silica showed it to be a mixture of the *trans* and *cis* oxiranes (202) and (212) followed by the *trans* oxirane (202) as a brown solid (0.55g; 34%), mp 155-158°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

Reactions of *Trans* 2-Benzoyl-3-(1-nitronaphth-2-yl)oxirane (202) with Stannic Chloride

(a) A solution of the oxirane (202) (3.2g; 0.01mol) in anhydrous toluene (75.0ml) was stirred and treated dropwise at room temperature with a solution of stannic chloride (2.8g; 0.011mol) in anhydrous toluene (25.0ml). The mixture was then stirred at room temperature with the exclusion of atmospheric moisture for 15min.

The resulting suspension was poured on to ice (100g) and the toluene layer was separated. The aqueous mother liquor was extracted several times with

dichloromethane. Rotary evaporation of the combined dichloromethane-toluene extracts gave a gummy red solid which was triturated with ether to afford 1,3-dihydro-1-(1-hydroxy-2-oxo-2-phenyl)ethyl-3-oxonaphth[1,2-c]isoxazole (214) as a red solid (47%) which formed pink microcrystals, mp 187-189°C (from ethyl acetate- light petroleum), ν_{\max} 3372 (OH), and 1746 and 1697 (C=O) cm^{-1} , $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.62-8.57 (1H, m, ArH), 8.32-8.27 (2H, m, ArH), 8.24-8.21 (1H, m, ArH), 8.19-8.06 (1H, m, ArH), 7.95-7.85 (3H, m, ArH), 7.76-7.62 (3H, m, ArH), 7.73 (1H, s, OH)(exch.), and 7.30 (1H, s, CH).

Found: C, 71.1; H, 4.4; N, 4.3%.

$\text{C}_{19}\text{H}_{13}\text{NO}_4$ requires: C, 71.5; H, 4.1; N, 4.4%.

Found: m/z (HRFABMS), 320.0926 [(M+H)⁺].

$\text{C}_{19}\text{H}_{13}\text{NO}_4$ requires: (M+H), 320.0923.

- (b) The reaction described in (a) before was repeated but in anhydrous dichloromethane and the resulting dark red- brown solution was poured on to ice (100g) then extracted several times with dichloromethane to give a dark red solid which was flash- chromatographed over silica.

Elution with dichloromethane-ethyl acetate (9:1) gave a gummy yellow solid which was triturated with ether to afford 2-benzoyl-4-oxo-4H-naphth[1,2-d]-1,3-oxazine (217) as a yellow solid (3%) which formed yellow microcrystals, mp 169-171°C (from ethanol), ν_{\max} 1754 and 1669 (C=O) cm^{-1} , $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.64-8.59 (1H, m, ArH), 8.34-8.25 (3H, m, ArH), 8.21-8.12 (2H, m, ArH), 7.90-7.77 (3H, m, ArH), and 7.71-7.63 (2H, m, ArH).

Found: C, 75.7; H, 3.5; N, 5.0%; m/z (HREIMS), 301.0741 (M⁺).

$\text{C}_{19}\text{H}_{11}\text{NO}_3$ requires: C, 75.7; H, 3.7; N, 4.7%; M, 301.0739.

Further elution with dichloromethane-ethyl acetate (9:1) gave 1,3-dihydro-3-oxonaphth[1,2-c]isoxazole (216) as a pinky red solid (65%) which formed light brown microcrystals, mp 141-143°C (from ethanol)(Lit.,⁸⁶ 193°C), ν_{\max} 3091 cm^{-1} (NH) and 1710 (C=O) cm^{-1} , $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 12.87 (1H, br s, NH)(exch.), 8.09-

7.99 (2H, m, ArH), 7.83-7.67 (2H, m, ArH), 7.75 (1H, s, ArH), and 7.74 (1H, s, ArH).

Found: C, 71.1; H, 3.8; N, 7.3%; m/z(EIMS), 185 (M^+).

$C_{11}H_7NO_2$ requires: C, 71.4; H, 3.8; N, 7.6%; M, 185.

Acetylation Reactions of 1,3-Dihydro-1-(1-hydroxy-2-oxo-2-phenyl)ethyl-3-oxonaphth[1,2-c]isoxazole (214)

- (a) The naphthisoxazole derivative (214) (0.32g; 0.001mol) was treated with acetic anhydride (0.3ml) and the mixture heated at 100°C (water bath) until it liquified. The resulting solution was then allowed to stand at room temperature for 20min.

The mixture was triturated with ether- ethyl acetate to afford the unreacted starting material (214) as an impure red solid (0.15g; 47%), mp 130-135°C, which gave the pure starting material (214) upon crystallisation from ethyl acetate- light petroleum, mp 185-187°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

Work up of the ether- ethyl acetate mother liquor gave no further identifiable material.

- (b) 1,3-Dihydro-1-(1-hydroxy-2-oxo-2-phenyl)ethyl-3-oxonaphth[1,2-c]isoxazole (214) (0.64g; 0.002mol) was treated with acetic anhydride (5.0ml) and the mixture heated under reflux with the exclusion of atmospheric moisture for 3h.

The resulting dark red solution was rotary evaporated under high vacuum (oil pump) to give a viscous dark red oil (0.7g) which was flash- chromatographed over silica.

Elution with hexane-dichloromethane (1:4) gave a gummy red- brown solid (0.2g) which was triturated with ether to afford 2-benzoyl-4-oxo-4H-naphth[1,2-d]-1,3-oxazine (217) as a pale orange- brown solid (0.17g; 28%) which formed yellow microcrystals, mp 167-169°C (from ethanol), identical (mp and IR spectrum) to a sample obtained before.

Alkaline Hydrolysis of 1,3-Dihydro-1-(1-hydroxy-2-oxo-2-phenyl)ethyl-3-oxonaphth[1,2-c]isoxazole (214)

The naphthisoxazole derivative (214) (0.32g; 0.001mol) was gently warmed with 2M aqueous sodium hydroxide solution (2.5ml) until all of the suspended solid dissolved.

The resulting red solution was then acidified by the dropwise addition of 2M aqueous hydrochloric acid and the precipitated solid collected and dried to give 1,3-dihydro-3-oxonaphth[1,2-c]isoxazole (216) as a pink solid (0.2g; 100%), mp 138-140°C, identified by comparison (mp, and IR and ¹H NMR spectra) with a sample obtained before.

1-Acetyl-1,3-dihydro-3-oxonaphth[1,2-c]isoxazole (218)

A solution of 1,3-dihydro-3-oxonaphth[1,2-c]isoxazole (216) (0.74g; 0.004mol) in anhydrous 1,4-dioxane (15.0ml) was stirred and treated at room temperature with triethylamine (0.5g; 0.68ml; 0.004mol) added in a single portion, then dropwise with a solution of acetyl chloride (0.34g; 0.0044mol) in anhydrous 1,4-dioxane (5.0ml). The mixture was then stirred at room temperature with the exclusion of atmospheric moisture for 0.5h.

The suspension was filtered to remove triethylamine hydrochloride and the 1,4-dioxane filtrate was rotary evaporated. The residual brown oil was treated with water (10.0ml) then extracted several times with dichloromethane to give a dark brown semi-solid which was triturated with ether to afford 1-acetyl-1,3-dihydro-3-oxonaphth[1,2-c]isoxazole (218) as a brown solid (0.6g; 66%) which formed brown microcrystals, mp 118-120°C (from ethyl acetate- light petroleum), ν_{\max} 1785, 1766 and 1727 (C=O) cm^{-1} , $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.58 (1H, d, J 8.4, ArH), 8.16 (1H, d, J 7.5, ArH), 8.03 (1H, d, J 8.5, ArH), 7.87-7.70 (3H, m, ArH), and 2.56 (3H, s, CH₃).

Found: C, 68.4; H, 4.0; N, 6.0%; m/z (HREIMS), 227.0576 (M^+).

$\text{C}_{13}\text{H}_9\text{NO}_3$ requires: C, 68.7; H, 4.0; N, 6.2%; M , 227.0582.

Alkaline Hydrolysis of 1-Acetyl-1,3-dihydro-3-oxonaphth[1,2-c]isoxazole (218)

The naphthisoxazole derivative (218) (0.45g; 0.002mol) was treated with 2M aqueous sodium hydroxide solution (5.0ml) and the resulting dark brown solution was just acidified by the dropwise addition of 2M aqueous hydrochloric acid.

The precipitated solid was collected to afford 1,3-dihydro-3-oxonaphth[1,2-c]isoxazole (216) as a brown solid (0.35g; 95%), mp 138-140°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

The Attempted Catalytic Hydrogenolysis of 1,3-Dihydro-3-oxonaphth[1,2-c]isoxazole (216)

The naphthisoxazole derivative (216) (0.37g; 0.002mol) was hydrogenated in ethanol (25.0ml) over palladium-on-charcoal (0.04g) at room temperature and atmospheric pressure until no further hydrogen was absorbed.

The mixture was filtered through Celite and the pad washed with warm ethanol. Rotary evaporation of the combined ethanol filtrate and washings and flash-chromatography of the brown semi- solid obtained gave unreacted starting material (216) (0.1g; 27%), mp 138-140°C as the only identifiable material.

Attempted Ammonolysis Reactions of 1,3-Dihydro-3-oxonaphth[1,2-c]isoxazole (216)

(a) A solution of the naphthisoxazole derivative (216) (0.37g; 0.002mol) in anhydrous 1,4-dioxane (7.5ml) was treated with a solution of piperidine (0.17g; 0.002mol) in anhydrous 1,4-dioxane (2.5ml) and the resulting mixture was stirred at room temperature for 45min.

The resulting brown solution was rotary evaporated under high vacuum (oil pump) to give a brown semi- solid which was treated with 2M aqueous hydrochloric acid (5.0ml) and extracted several times with dichloromethane. Rotary evaporation of the combined dichloromethane extracts gave the unreacted 1,3-dihydro-3-oxonaphth[1,2-c]isoxazole (216) as a dark brown solid (0.4g;

100%), mp 133-137°C, which was identified by comparison (mp and IR spectrum) with a sample obtained before.

- (b) A solution of the naphthisoxazole derivative (216) (0.37g; 0.002mol) in anhydrous 1,4-dioxane (7.5ml) was mixed with a solution of aniline (0.19g; 0.002mol) in anhydrous 1,4-dioxane (2.5ml) and the resulting solution was stirred at room temperature for 30min, then at 50°C for 30min and finally heated under reflux for 30min.

The dark red- brown solution was rotary evaporated under high vacuum (oil pump). The gummy dark brown solid obtained was triturated with ether to afford the unreacted starting material (216) as a dark brown solid (0.33g; 89%), mp 138-140°C, which was identified by comparison (mp and IR spectrum) with a sample obtained before.

The Attempted Oxidation of 2-Methyl-1-nitronaphthalene (181) with Chromium Trioxide

A solution of 2-methyl-1-nitronaphthalene (181) (0.37g; 0.002mol) in 70% v/v aqueous glacial acetic acid (20.0ml) was stirred and treated at room temperature with small portions of solid chromium trioxide (0.74g). The mixture was then heated at 100°C for 0.5h..

The dark red solution was rotary evaporated under high vacuum and the dark red-brown residue was treated with water (5.0ml) and filtered. The pale green- yellow solid obtained was treated with 10% w/v aqueous sodium hydrogen carbonate solution (5.0ml) and stirred at room temperature for 30min. The resulting suspension was filtered to afford the unreacted starting material (181) as a pale green- yellow solid (0.27g; 73%), mp 76-79°C (Lit.,⁸¹ 79-82°C), identified by comparison (mp and IR spectrum) with an authentic sample.

Attempted Oxidation Reactions of 1-(N,N-Dimethylamino)-2-(1-nitronaphth-2-yl)ethene (182)

- (a) A suspension of the enamine (182) (0.48g; 0.002mol) in 1M aqueous sodium hydroxide solution (5.0ml) was stirred, cooled to 0-5°C (ice-salt bath) and treated dropwise with 30% w/v aqueous hydrogen peroxide solution (1.0ml) at such a rate that the temperature was < 5°C. The mixture was then stirred at room temperature for 3h.

The resulting red suspension was filtered to afford the unreacted enamine (182) as a red solid (0.46g; 96%), mp 96-98°C (Lit.,⁸² 98-100°C), which was identified by comparison (mp and IR spectrum) with a sample obtained before.

- (b) A solution of the enamine (182) (0.48g; 0.002mol) in 1,4-dioxane (10.0ml) was stirred and treated with aqueous sodium hypochlorite solution (14-15% available chlorine; ca.2M)(5.0ml; 0.01mol). The mixture was then stirred at room temperature for 10min.

The resulting dark red solution was rotary evaporated at as low a temperature as possible and the residue was treated with water (5.0ml) then extracted several times with dichloromethane. Rotary evaporation of the combined dichloromethane extracts gave a red oil which was triturated with ether to afford the unreacted enamine (182) as a red solid (0.46g; 96%), mp 97-99°C (Lit.,⁸² 98-100°C), which was identified by comparison (mp and IR spectrum) with a sample obtained before.

2-(1-Nitronaphth-2-yl)acetic Acid (220)

A solution of 1-(N,N-dimethylamino)-2-(1-nitronaphth-2-yl)ethene (182) (0.48g; 0.002mol) in 70% v/v aqueous glacial acetic acid (20.0ml) was stirred and treated at room temperature with small portions of solid chromium trioxide (0.96g) and the mixture was then heated at 100°C for 0.5h.

The dark red solution was rotary evaporated under high vacuum (oil pump) and the dark brown- red residue was treated with water (5.0ml) and filtered to give 2-(1-nitronaphth-2-yl)acetic acid (220) as a pale green solid (0.33g; 71%) which formed

green-yellow microcrystals, mp 170-172°C (decomp.) (from ethanol- light petroleum), ν_{\max} 3700-2300 br (OH), 1708 (C=O), and 1514 and 1348 (NO₂) cm⁻¹, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.21-8.12 (2H, m, ArH), 7.95-7.62 (4H, m, ArH), 3.86 (2H, s, CH₂), and 3.43 (1H, br s, OH)(exch.).

Found: C, 61.5; H, 4.1; N, 5.9%; m/z(HREIMS), 231.0535 (M⁺).

C₁₂H₉NO₄ requires: C, 62.3; H, 3.9; N, 6.1%; M, 231.0532.

1-Nitronaphthalene-2-carboxylic Acid (219)

A solution of 1-nitro-2-naphthaldehyde (183) (0.4g; 0.002mol) in 70% v/v aqueous glacial acetic acid (20.0ml) was stirred and treated at room temperature with small portions of solid chromium trioxide (0.8g). The mixture was then heated at 100°C for 0.5h.

The resulting dark red solution was rotary evaporated under high vacuum (oil pump) and the residue was treated with water (5.0ml) and filtered to afford 1-nitronaphthalene-2-carboxylic acid (219) as a green- yellow solid (0.4g; 93%) which formed pale green- yellow microcrystals, mp 232-234°C (from ethanol- light petroleum)(Lit.,⁸⁷ 239°C), ν_{\max} 3500-2100 br (OH), 1693 (C=O), and 1535 and 1378 (NO₂) cm⁻¹, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.28-8.20 (2H, m, ArH), 8.05-8.02 (1H, m, ArH), 7.81 (1H, br s, ArH), 7.74-7.73 (2H, m, ArH), and 4.02 (1H, br s, OH)(exch.).

Found: m/z(HREIMS), 217.0381 (M⁺).

C₁₁H₇NO₄ requires: M, 217.0375.

Attempted Reduction Reactions of 1-Nitronaphthalene-2-carboxylic Acid (219)

Using Zinc in the Presence of Ammonium Chloride

(a) A solution of the nitronaphthalene carboxylic acid (219) (0.87g; 0.004mol) in tetrahydrofuran (25.0ml) was stirred and cooled to 0°C (ice- salt bath) then treated with a solution of ammonium chloride (1.5g; 0.028mol) in water (6.0ml) followed at 0-5°C with zinc dust (0.55g; 0.0084g.atom) added slowly in small

portions to the vigorously stirred solution. The mixture was then stirred at 0-5°C for 4h.

The suspension was filtered and the inorganic residue washed several times with ethyl acetate. The aqueous- ethyl acetate filtrate was extracted several times with ethyl acetate to give an intractable brown solid (0.73g), mp >300°C, which resisted characterisation and was not further investigated.

- (b) A suspension of the nitronaphthalene carboxylic acid (219) (1.1g; 0.005mol) in water (5.0ml) was stirred and neutralised with solid barium hydroxide (0.8g). The resulting suspension was diluted with water (2.5ml) and cooled to 10°C (ice-bath) then treated with ammonium chloride (0.4g), added in one portion, followed by zinc dust (0.75g) added in portions at such a rate that the reaction temperature was < 20°C. The suspension was then stirred at 10-20°C for 0.5h.

The grey suspension was filtered and the zinc residue was washed with warm water (2.5ml). The aqueous filtrate and washings were poured on to ice (2.5g) and the red solution was acidified to pH 1 with 50% v/v aqueous hydrochloric acid. The resulting suspension was cooled in a fridge for 2h then filtered to afford the unreacted starting material (219) as a light brown solid (0.1g; 9%), mp 227-229°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

Further work up of the aqueous mother liquor gave no other identifiable material.

1-Aminonaphthalene-2-carboxylic Acid (222)

- (a) A solution of the nitronaphthalene carboxylic acid (219) (0.87g; 0.004mol) in ethanol (40.0ml) was hydrogenated over palladium-on-charcoal catalyst (0.09g) at room temperature and atmospheric pressure until no further hydrogen was absorbed.

The mixture was filtered through Celite and the pad washed with warm ethanol. Rotary evaporation of the combined ethanol filtrate and washings gave 1-aminonaphthalene-2-carboxylic acid (222) as a light brown solid (0.66g; 88%) which formed light brown microcrystals, mp 185-187°C (from ethyl

acetate)(Lit., ⁸⁸ 205°C), ν_{\max} 3487 and 3352 (NH), 3300-2000 br (OH), and 1662 (C=O) cm^{-1} , $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.32 (1H, d, J 7.7, ArH), 7.75 (2H, d, J 8.6, ArH), 7.56-7.46 (2H, m, ArH), and 6.98 (1H, d, J 8.6, ArH).

Found: C, 70.4; H, 4.8; N, 7.5%; m/z (EIMS), 187 (M^+).

$\text{C}_{11}\text{H}_9\text{NO}_2$ requires: C, 70.6; H, 4.8; N, 7.5%; M, 187.

- (b) A solution of 1-nitronaphthalene-2-carboxylic acid (219) (0.87g; 0.004mol) in anhydrous dimethylformamide (20.0ml), was hydrogenated over Raney nickel (50% slurry in water)(0.17g; 0.09g. atom) at room temperature and atmospheric pressure until no further hydrogen was absorbed.

The mixture was filtered through Celite and the pad was washed with warm anhydrous dimethylformamide. Rotary evaporation of the combined dimethylformamide filtrate and washings under high vacuum (oil pump) gave a red- brown oil (1.0g) which was triturated with ethyl acetate to afford 1-aminonaphthalene-2-carboxylic acid (222) as a dark brown solid (0.55g; 74%), mp 181-183°C, which was identified by comparison (mp and IR spectrum) with a sample obtained before.

- (c) A suspension of 10% palladium-on-charcoal (0.02g) in water (4.0ml) was stirred under nitrogen and treated at room temperature with a solution of sodium borohydride (0.28g; 0.008mol) in water (6.0ml), followed by a solution of the nitro- acid (219) (0.87g; 0.004mol) in methanol (20.0ml). The mixture was then stirred at room temperature under nitrogen for a further 10min after the addition was complete.

The resulting suspension was filtered through Celite and the pad washed with several small portions of methanol. The combined methanol filtrate and washings were concentrated by rotary evaporation and the aqueous residue was diluted with water (5.0ml) then neutralised by the addition of 2M aqueous hydrochloric acid and solid anhydrous sodium acetate. The resulting brown suspension was filtered to afford the amino- acid (222) as a brown solid (0.25g; 33%), mp 182-

184°C, which was identified by comparison (mp and IR spectrum) with a sample obtained before.

2-Methyl-4-oxo-4H-naphth[1,2-d]-1,3-oxazine (223)

1-Aminonaphthalene-2-carboxylic acid (222) (0.37g; 0.002mol) was heated under reflux with acetic anhydride (5.0ml) with the exclusion of atmospheric moisture for 1h.

The resulting brown solution was rotary evaporated under high vacuum (oil pump) and the gummy brown solid obtained was triturated with ether to afford the naphthoxazine derivative (223) as a light brown solid (0.34g; 81%) which formed brown microcrystals, mp 179-181°C (from ethanol)(Lit.,⁸⁹ 178°C), ν_{\max} 1736 (C=O) cm^{-1} , $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.75 (1H, d, J 8.2, ArH), 8.10-7.94 (3H, m, ArH), 7.86-7.73 (2H, m, ArH), and 2.54 (3H, s, CH_3).

Found: C, 73.5; H, 4.0; N, 6.5%; $m/z(\text{HREIMS})$, 211.0627 (M^+).

$\text{C}_{13}\text{H}_9\text{NO}_2$ requires: C, 73.9; H, 4.3; N, 6.6%; M , 211.0633.

Methyl 1-Nitronaphthalene-2-carboxylate (224)

(a) 1-Nitronaphthalene-2-carboxylic acid (219) (0.87g; 0.004mol) was treated with thionyl chloride (4.0ml) and the mixture was stirred and heated at 100°C (oil bath) with the exclusion of atmospheric moisture for 2h. The dark red- brown solution was rotary evaporated and the residue was treated with methanol (5.0ml) then heated under reflux for 1h.

The resulting dark red solution was rotary evaporated and the viscous red- brown oil obtained was flash- chromatographed over silica, eluting with hexane- dichloromethane (2:3) to give the ester derivative (224) as a cream solid (0.1g; 11%) which formed cream microcrystals, mp 135-137°C (from ethanol), ν_{\max} 1720 (C=O) cm^{-1} , $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.35-8.31 (1H, m, ArH), 8.24-8.18 (1H, m, ArH), 8.02 (1H, d, J 8.6, ArH), 7.88-7.72 (3H, m, ArH), and 3.91 (3H, s, CH_3).

Found: C, 62.2; H, 3.9; N, 5.9%; m/z(EIMS), 231 (M^+).
C₁₂H₉NO₄ requires: C, 62.3; H, 3.9; N, 6.1%; M, 231.

(b) A solution of 1-nitronaphthalene-2-carboxylic acid (219) (8.7g; 0.04mol) in methanol (60.0ml) was stirred, cooled in an ice- water bath and carefully treated dropwise with concentrated sulphuric acid (4.0ml). The mixture was then stirred and heated under reflux with the exclusion of atmospheric moisture for 6h.

The suspension was cooled then concentrated by rotary evaporation at as low a temperature as possible and the residue was carefully diluted with water (80.0ml) and extracted several times with dichloromethane. The combined dichloromethane extracts were washed with 2M aqueous sodium hydroxide solution (2 x 40.0ml) then with water (40.0ml) and rotary evaporated to give the ester derivative (224) as a pink solid (7.2g; 78%), mp 134-136°C, which was identified by comparison (mp and IR spectrum) with a sample obtained in (a) before.

1,3-Dihydro-3-oxonaphth[1,2-c]isoxazole (216)

A solution of methyl 1-nitronaphthalene-2-carboxylate (224) (6.9g; 0.03mol) in tetrahydrofuran (150.0ml) was stirred and cooled to 0°C (ice- salt bath) then treated with a solution of ammonium chloride (11.2g; 0.21mol) in water (40.0ml), followed at 0-5°C by zinc dust (4.1g; 0.06g.atom) added slowly in small portions to the vigorously stirred solution. The suspension was then stirred at 0-5°C for 1h.

The suspension was filtered and the inorganic residue was washed several times with ethyl acetate then water. The combined ethyl acetate- aqueous filtrate and washings were extracted several times with ethyl acetate to give a gummy brown solid which was triturated with ether to afford the naphthisoxazole derivative (216) as a brown solid (4.6g; 83%), mp 135-137°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

Attempted Reactions of 1,3-Dihydro-3-oxonaphth[1,2-c]isoxazole (216) with 2-Oxophenylacetaldehyde (228)

- (a) A suspension of the naphthisoxazole derivative (216) (0.37g; 0.002mol) and 2-oxophenylacetaldehyde (228) (0.27g; 0.002mol) in water (10.0ml) was stirred and heated at 60°C (oil bath) for 15min.

The suspension was allowed to cool then filtered to afford the unreacted naphthisoxazole (216) as a brown solid (0.34g; 92%), mp 137-139°C, which was identified by comparison (mp and IR spectrum) with a sample obtained before.

- (b) A solution of the naphthisoxazole derivative (216) (0.37g; 0.002mol) in anhydrous 1,4-dioxane (7.5ml) was treated with a solution of 2-oxophenylacetaldehyde (228) (0.27g; 0.002mol) in anhydrous 1,4-dioxane (2.5ml) and the resulting solution was stirred and heated at 50°C for 30min, then at 100°C for 30min, and finally under reflux for 30min.

The dark red- brown solution was rotary evaporated to give a dark red oil which was triturated with ether to afford the unreacted naphthisoxazole derivative (216) as a brown solid (0.3g; 81%), mp 138-140°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

- (c) A solution of the naphthisoxazole derivative (216) (0.37g; 0.002mol) in anhydrous 1,4-dioxane (7.5ml) was stirred and treated at room temperature with triethylamine (0.25g; 0.34ml; 0.002mol) added in a single portion, followed by the dropwise addition of a solution of 2-oxophenylacetaldehyde (228) (0.29g; 0.0022mol) in anhydrous 1,4-dioxane (2.5ml). The resulting red solution was then stirred at room temperature with the exclusion of atmospheric moisture for 0.5h.

The red solution was rotary evaporated under high vacuum (oil pump) and the residual dark red oil was treated with water (5.0ml) then extracted several times with dichloromethane to give a red oil which was flash- chromatographed over silica.

Elution with dichloromethane-ethyl acetate (9:1) gave the unreacted naphthisoxazole derivative (216) as a light brown solid (0.4g; 100%), mp 138-140°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

Reactions of *Trans* 2-Benzoyl-3-(1-nitronaphth-2-yl)oxirane (202) with Boron Trifluoride Etherate

- (a) A solution of the *trans* oxirane (202) (3.2g; 0.01mol) in anhydrous 1,2-dimethoxyethane (75.0ml) was stirred and treated dropwise at room temperature with a solution of boron trifluoride etherate (6.0g; 5.0ml; 0.04mol) in anhydrous 1,2-dimethoxyethane (25.0ml). The mixture was then stirred at room temperature with the exclusion of atmospheric moisture for 15min.

The resulting dark red- brown solution was poured on to ice (40g) and extracted several times with dichloromethane to give a gummy brown solid which was flash- chromatographed over silica.

Elution with hexane-dichloromethane (2:3) gave a gummy light brown solid which was triturated with ether to afford the unreacted starting material (202) as a light brown solid (1.6g; 50%), mp 159-161°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

Further elution with dichloromethane gave 1,3-dihydro-3-oxonaphth[1,2-c]isoxazole (216) as a dark red- brown solid (0.33g; 18%), mp 140-142°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

- (b) Repetition of the reaction described in (a) before but under reflux for 15min followed by the same work up gave a dark brown oil which was triturated with ether to afford 1,3-dihydro-1-(1-hydroxy-2-oxo-2-phenyl)ethyl-3-oxonaphth[1,2-c]isoxazole (214) as a brown solid (1.8g; 56%), mp 185-187°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

Rotary evaporation of the ethereal mother liquor gave a dark brown oil which was flash- chromatographed over silica eluting with dichloromethane to give 1,3-dihydro-3-oxonaphth[1,2-c]isoxazole (216) as a brown solid (0.59g; 32%), mp 140-142°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

- (c) Repetition of the reaction described in (a) before but in dichloromethane as solvent followed by the same work up gave a brown solid which was flash-chromatographed over silica.

Elution with dichloromethane afforded 2-oxophenylacetaldehyde (228) as an orange oil (1.3g; 93%), identified by comparison (IR spectrum) with an authentic sample.

Further elution with dichloromethane afforded 1,3-dihydro-3-oxonaphth[1,2-c]isoxazole (216) as a brown solid (1.8g; 95%), mp 136-139°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

- (d) Repetition of the reaction described in (c) before but under reflux for 15min followed by the same work up gave a dark brown solid which was flash-chromatographed over silica.

Elution with dichloromethane afforded 2-oxophenylacetaldehyde (228) as a viscous orange oil (1.0g; 95%), identified by comparison (IR spectrum) with an authentic sample.

Further elution with dichloromethane afforded 1,3-dihydro-3-oxonaphth[1,2-c]isoxazole (216) as a brown solid (1.9g; 100%), mp 135-137°C, identified by comparison (mp and IR spectrum) with an authentic sample obtained before.

The Reaction of 1,3-Dihydro-1-(1-hydroxy-2-oxo-2-phenyl)ethyl-3-oxonaphth[1,2-c]isoxazole (214) with Boron Trifluoride Etherate

A solution of the 3-oxonaphthisoxazole derivative (214) (0.64g; 0.002mol) in anhydrous 1,2-dimethoxyethane (15.0ml) was stirred at room temperature and treated dropwise with a solution of boron trifluoride etherate (1.2g; 1.0ml; 0.008mol) in

anhydrous 1,2-dimethoxyethane (5.0ml). The solution was then stirred and heated under reflux with the exclusion of atmospheric moisture for 15min.

The resulting brown solution was poured on to ice (20g) and extracted several times with dichloromethane to give a dark brown oil which was triturated with ether-dichloromethane to afford the unreacted starting material (214) as a brown solid (0.3g; 47%), 184-186°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

Rotary evaporation of the ether- dichloromethane mother liquor gave a viscous dark brown oil (0.38g) which was flash- chromatographed over silica.

Elution with dichloromethane gave 1,3-dihydro-3-oxonaphth[1,2-c]isoxazole (216) as a brown solid (0.14g; 38%), mp 139-141°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

The Reaction of 1,3-Dihydro-1-(1-hydroxy-2-oxo-2-phenyl)ethyl-3-oxonaphth[1,2-c]isoxazole (214) with Silicagel

A solution of the 3-oxonaphthisoxazole derivative (214) (0.32g; 0.001mol) in anhydrous dichloromethane (10.0ml) was treated with silicagel (2.0g) and the suspension was stirred at room temperature for 1h.

The brown suspension was filtered and the silicagel residue was washed with a little dichloromethane. Rotary evaporation of the dichloromethane filtrate and washings gave a gummy brown solid which was triturated with ether to afford 1,3-dihydro-3-oxonaphth[1,2-c]isoxazole (216) as a brown solid (0.17g; 92%), mp 138-140°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

Rotary evaporation of the ethereal mother liquor gave 2-oxophenylacetaldehyde (228) as a red oil (0.13g; 100%), identified by comparison (IR spectrum) with an authentic sample.

3-Methyl-2-nitrothiophene (233)

Acetic anhydride (100ml) was cooled to 0°C (ice-salt bath) and treated dropwise with stirring with fuming nitric acid (d=1.52)(64.0g; 1.0mol) at such a rate that the

reaction temperature was $< 5^{\circ}\text{C}$. The resulting nitrating mixture was then cooled to -15 to -12°C (ice-solid CO_2 bath) and rapidly treated at this temperature over 2h with stirring, with a solution of 3-methylthiophene (232) (39.2g; 0.4mol) in acetic anhydride (100ml).

The red solution was poured on to ice (600g) and extracted several times with ether. The combined ether extracts were washed with 10% w/v aqueous sodium hydrogen carbonate solution (4 x 200ml) and rotary evaporated to give a red liquid which was cooled and triturated with light petroleum to afford 3-methyl-2-nitrothiophene (233) as a yellow solid (22.2g, 39%), mp $57-60^{\circ}\text{C}$ (lit.,⁹⁰ $61-63^{\circ}\text{C}$).

Rotary evaporation of the ethereal mother liquor gave a red oil which was flash-chromatographed over silica eluting with hexane-dichloromethane (1:1) to obtain a second crop of 3-methyl-2-nitrothiophene (233) (8.1g; 14%), mp $58-61^{\circ}\text{C}$, identified by comparison (mp and IR spectrum) with a sample obtained before.

1-(N,N-Dimethylamino)-2-(2-nitrothien-3-yl)ethene (234)

A solution of 3-methyl-2-nitrothiophene (233) (17.9g; 0.125mol) in anhydrous dimethylformamide (100ml) was stirred and treated with a solution of N,N-dimethylformamide dimethyl acetyl (30.0g; 0.25mol) in anhydrous dimethylformamide (100ml) and the mixture stirred and heated under reflux with the exclusion of atmospheric moisture for 18h.

The resulting red solution was rotary evaporated under high vacuum (oil pump) to give a red oil which was triturated with ether-ethanol to afford the enamine (234) as a dark red solid (22.0g; 89%), which formed red microcrystals, mp $130-132^{\circ}\text{C}$ (from ethyl acetate-light petroleum), ν_{max} 1536 and 1377 (NO_2) cm^{-1} , $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 7.91 (1H, d, J 13.3, CH), 7.63 (1H, d, J 6.0, ArH), 7.39 (1H, d, J 6.0, ArH), 6.34 (1H, d, J 13.3, CH), and 3.33 (6H, s, 2 x CH_3).

Found: C, 49.3; H, 5.5; N, 13.9%; m/z (HREIMS), 198.0462 (M^+).

$\text{C}_8\text{H}_{10}\text{N}_2\text{O}_2$ ^{32}S requires: C, 48.5; H, 5.1; N, 14.1%; M, 198.0463.

2-Nitrothiophene-3-carboxaldehyde (235)

A suspension of the enamine (234) (27.7g; 0.14mol) in tetrahydrofuran (700.0ml) was stirred and treated with a solution of sodium periodate (89.9g; 0.42mol) in water (700.0ml) added in one portion. The mixture was then stirred at room temperature for 30min.

The mixture was filtered and the insoluble inorganic residue was washed several times with ethyl acetate. The filtrate and washings were separated and the aqueous layer washed several times with ethyl acetate. The combined ethyl acetate extracts were washed with 10% w/v aqueous sodium hydrogen carbonate solution (3 x 280ml) and rotary evaporated to give a brown oil which was flash- chromatographed over silica, eluting with hexane-dichloromethane (3:2) to obtain 2-nitrothiophene-3-carboxaldehyde (235) as a brown solid (13.0g; 59%), mp 54-56°C (lit.,⁹¹ 56-57°C) which was used without further purification.

1,1-Diacyl-2-(2-nitrothienyl-3-yl)ethenes (236)

(a) Solutions of 2-nitrothiophene-3-carboxaldehyde (235) (1.6g; 0.01mol) in anhydrous ether (90.0ml) and the respective active methylene compound (136) (0.01mol) in anhydrous ether (10.0ml) were mixed, stirred, and cooled to 0°C (ice- salt bath) then treated with a slow stream of hydrogen chloride until saturated. The mixture was securely stoppered and stored in a fridge for 19h.

The mixture was rotary evaporated and the oil obtained purified to give the product as described for the individual reactions below.

(i) The oil obtained from the reaction of 2-nitrothiophene-3-carboxaldehyde (235) with pentane-2,4-dione (136a) was triturated with ether to afford 3-acetyl-4-(2-nitrothien-3-yl)but-3-en-2-one (236a) as a light brown solid (84%), which formed light brown plates, mp 88-90°C (from ethanol), ν_{\max} 1715 (C=O), and 1524 and 1374 (NO₂) cm⁻¹, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.00 (1H, d, J 5.2, ArH), 8.00 (1H, s, CH), 7.03 (1H, d, J 5.0, ArH), 2.45 (3H, s, CH₃), and 2.26 (3H, s, CH₃).

Found: C, 49.9; H, 4.1; N, 6.0%; m/z(FABMS), 240 [(M+H)⁺].

C₁₀H₉NO₄S requires: C, 50.2; H, 3.8; N, 5.9%; M, 239.

- (ii) The oil obtained from the reaction of 2-nitrothiophene-3-carboxaldehyde (235) with 1-phenylbutane-1,3-dione (136b) was treated with water (10.0ml) and extracted several times with dichloromethane to give 3-benzoyl-4-(2-nitrothienyl-3-yl)but-3-en-2-one (236b) as a light brown solid (100%) which formed light brown microcrystals, mp 112-114°C (from ethanol), ν_{\max} 1672 and 1661 (C=O), and 1592 and 1373 (NO₂) cm⁻¹, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.35 (1H, s, CH), 7.86-7.78 (3H, m, ArH), 7.66-7.61 (1H, m, ArH), 7.54-7.46 (2H, m, ArH), 6.80 (1H, dd, J 5.5 and 0.5, ArH), and 2.54 (3H, s, CH₃).

Found: C, 59.6; H, 3.8; N, 4.6%; m/z(APCIMS), 302 [(M+H)⁺].

C₁₅H₁₁NO₄S requires: C, 59.8; H, 3.7; N, 4.7%; M, 301.

- (iii) The oil obtained from the reaction of 2-nitrothiophene-3-carboxaldehyde (235) with 1,3-diphenylpropane-1,3-dione (136c) was treated with water (10.0ml) and extracted several times with dichloromethane to give a red oil which was flash- chromatographed over silica.

Elution with hexane-ether (3:2) gave unreacted 1,3-diphenylpropane-1,3-dione (136c) as an orange solid (59%), mp 75-77°C, identified by comparison (mp and IR spectrum) with an authentic sample.

Further elution with hexane-ether (3:2) gave unreacted 2-nitrothiophene-3-carboxaldehyde (235) as a brown solid (44%), mp 53-55°C, identified by comparison (mp and IR spectrum) with a sample prepared before.

- (iv) The oil obtained from the reaction of 2-nitrothiophene-3-carboxaldehyde (235) with ethyl 3-oxobutanoate (136d) was treated with water (10.0ml) and extracted several times with dichloromethane to give a dark red oil which was flash- chromatographed over silica.

Elution with hexane-dichloromethane (2:3) afforded E or Z ethyl 2-acetyl-3-(2-nitrothien-3-yl)prop-2-enoate (236d) as a yellow solid (13%), which formed pale yellow microcrystals, mp 63-65°C, (from ethyl acetate-light

petroleum), ν_{\max} 1707 (C=O), and 1519 and 1386 (NO₂) cm⁻¹, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.01 (1H, s, CH), 8.00 (1H, d, J 5.3, ArH), 7.03 (1H, dd, J 5.6 and 0.6, ArH), 4.29 (2H, q, J 7.1, CH₂), 2.36 (3H, s, CH₃), and 1.27 (3H, t, J 7.1, CH₃).

Found: C, 49.1; H, 4.0; N, 5.1%; m/z(FABMS), 270 [(M+H)⁺].
C₁₁H₁₁NO₅S requires: C, 49.1; H, 4.1; N, 5.2%; M, 269.

Further elution with hexane-dichloromethane (2:3) gave a mixture of *E* and *Z* ethyl 2-acetyl-3-(2-nitrothien-3-yl)prop-2-enoate (236d) as a yellow solid (67%), which formed pale yellow microcrystals, mp 67-69°C (from ethyl acetate- light petroleum), ν_{\max} 1722 and 1665 (C=O), and 1377 (NO₂) cm⁻¹, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.11 (1H, s, CH), 8.04 (1H, d, J 5.5, ArH), 8.03 (1H, d, J 5.9, ArH), 7.98 (1H, s, CH), 7.10 (1H, d, J 5.5, ArH), 7.03 (1H, d, J 5.6, ArH), 4.29 (2H, q, J 7.1, CH₂), 4.18 (2H, q, J 7.1, CH₂), 2.45 (3H, s, CH₃), 2.36 (3H, s, CH₃), 1.27 (3H, t, J 7.1, CH₃), and 1.13 (3H, t, J 7.1, CH₃).

Found: C, 49.0; H, 3.9; N, 5.1%; m/z(FABMS), 270 [(M+H)⁺].
C₁₁H₁₁NO₅S requires: C, 49.1; H, 4.1; N, 5.2%; M, 269.

- (b) A mixture of 2-nitrothiophene-3-carboxaldehyde (235) (0.8g; 0.005mol), 1,3-diphenylpropane-1,3-dione (136c) (1.4g; 0.006mol), and glacial acetic acid (0.4ml) was stirred and treated at room temperature with piperidine (0.5ml) added in one portion. The mixture was then stirred at room temperature with the exclusion of atmospheric moisture for 2h.

The mixture was diluted with water (5.0ml) and extracted several times with dichloromethane to give a brown solid which was flash- chromatographed over silica eluting with hexane-dichloromethane (3:7) to give 2-benzoyl-3-(2-nitrothien-3-yl)-1-phenylprop-2-en-1-one (236c) as a yellow solid (77%), which formed yellow microcrystals, mp 159-161°C (from ethanol), ν_{\max} 1675 (C=O), and 1514 and 1325 (NO₂) cm⁻¹, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.02-7.85 (6H, m, ArH plus CH), 7.78-7.48 (6H, m, ArH), and 6.93 (1H, d, J 5.6, ArH).

Found: C, 65.9; H, 3.7; N, 3.8%; m/z(APCIMS), 364 [(M+H)⁺].
C₂₀H₁₃NO₄S requires: C, 66.1; H, 3.6; N, 3.9%; M, 363.

(c) A solution of 2-nitrothiophene-3-carboxaldehyde (235) (0.8g; 0.005mol) and pentane-2,4-dione (136a) (0.6g; 0.006mol) in anhydrous ethanol (15.0ml) was stirred and treated with a solution of glacial acetic acid (0.4ml; 0.4g; 0.0065mol) in anhydrous ethanol (5.0ml). A solution of piperidine (0.5ml; 0.43g; 0.005mol) in anhydrous ethanol (5.0ml) was then added and the mixture stirred and heated under reflux with the exclusion of atmospheric moisture for 2h.

The dark red- brown solution was rotary evaporated to give a dark red oil which was flash- chromatographed over silica eluting with dichloromethane-ethyl acetate (9:1) gave 3-acetyl-4-(2-nitrothien-3-yl)but-3-en-2-one (236a) as a beige solid (0.07g; 6%), mp 83-86°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

Trans 2-Benzoyl-3-(2-nitrothien-3-yl)oxirane (241)

A suspension of 2-nitrothiophene-3-carboxaldehyde (235) (0.79g; 0.005mol) and 2-bromoacetophenone (1.0g; 0.005mol) in methanol (15.0ml) was stirred and cooled to 0-10°C (ice bath) then treated dropwise with a solution of sodium (0.12g; 0.005g.atom) in methanol (5.0ml). The mixture was then stirred at room temperature with the exclusion of atmospheric moisture for 3h.

The suspension was acidified to pH 6 by the addition of glacial acetic acid and then filtered to afford the oxirane derivative (241) as a cream solid (1.1g; 80%), which formed cream microcrystals, mp 145-147°C (from ethanol), ν_{\max} 1681 (C=O), and 1544 and 1374 (NO₂) cm⁻¹, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.12-8.03 (3H, m, ArH), 7.76-7.69 (2H, m, ArH), 7.60-7.54 (1H, m, ArH), 7.16 (1H, d, J 5.4, ArH), 4.88 (1H, d, J 2.0, CH), and 4.65 (1H, d, J 2.0, CH).

Found: C, 56.8; H, 3.3; N, 5.1%; m/z(FABMS), 276 [(M+H)⁺].
C₁₃H₉NO₄S requires: C, 56.7; H, 3.3; N, 5.1%; M, 275.

Reactions of *Trans* 2-Benzoyl-3-(2-nitrothien-3-yl)oxirane (241) with Hydrogen Chloride

- (a) A solution of the oxirane (241) (1.1g; 0.004mol) in anhydrous 1,4-dioxane (50.0ml) was stirred and cooled to 11°C (ice- water bath) and treated with a slow stream of hydrogen chloride until saturated. The mixture was then securely stoppered and stored in a fridge for 24h.

The resulting yellow solution was rotary evaporated and the residue treated with 10% w/v aqueous sodium hydrogen carbonate solution (5.0ml) and extracted several times with dichloromethane to give an orange semi- solid which was flash- chromatographed over silica.

Elution with hexane-dichloromethane (2:3) gave 1-(2-nitrothien-3-yl)-3-phenylpropane-1,3-dione (244) as a mixture of enol tautomers (0.45g; 41%), which formed yellow microcrystals, mp 98-100°C (from ethanol), ν_{\max} 3334 (OH), 1650 (C=O), and 1517 and 1376 (NO₂) cm⁻¹, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 10.96 (1H, br s, OH)(exch.), 8.04-7.95 (2H, m, ArH), 7.84-7.80 (2H, m, ArH), 7.76-7.67 (1H, m, ArH), 7.60-7.54 (2H, m, ArH), and 7.09 (1H, s, CH)(exch.), $\delta_{\text{C}}[(\text{CD}_3)_2\text{SO}]$ 196.9 (quat.)(isomer a), 193.2 (quat.)(isomer b), 190.4 (quat.)(isomer a), 152.8 (quat.)(isomer b), 152.7 (quat.)(isomer b), 145.7 (quat.)(isomer a), 137.7 (quat.)(isomer a), 137.2 (quat.)(isomer b), 137.1 (quat.)(isomer a), 136.2 (quat.)(isomer b), 135.0 (CH)(isomer a), 133.3 (CH)(isomer a), 133.1 (CH)(isomer b), 133.0 (CH)(isomer b), 132.2 (CH)(isomer a), 131.6 (CH)(isomer a), 130.3 (2 x CH)(isomer a), 130.0 (CH)(isomer b), 129.4 (2 x CH)(isomer b), 129.1 (2 x CH)(isomer a), 128.6 (2 x CH)(isomer b), and 106.2 (CH)(isomer b).

Found: C, 56.6; H, 3.3; N, 5.0%; m/z (FABMS), 276 [(M+H)⁺].

C₁₃H₉NO₄S requires: C, 56.7; H, 3.3; N, 5.1%; M, 275.

Further elution with hexane-dichloromethane (2:3) afforded 1-benzoyl-1-chloro-2-hydroxy-2-(2-nitrothien-3-yl)ethane (245) as a yellow solid (0.15g; 12%),

which formed yellow microcrystals, mp 101-103°C (from ethyl acetate- light petroleum), ν_{\max} 3439 (OH), 1678 (C=O), and 1537 and 1402 (NO₂) cm⁻¹, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.14-8.09 (2H, m, ArH), 7.98 (1H, dd, J 5.6 and 0.2, ArH), 7.76-7.66 (1H, m, ArH), 7.61-7.51 (3H, m, ArH), 6.58 (1H, d, J 5.5, OH)(exch.), 6.19-6.12 (1H, m, CH), and 5.77 (1H, d, J 8.6, CH).

Found: C, 50.4; H, 3.3; N, 4.6%; m/z(EIMS), 313, 311 (M⁺).

C₁₃H₁₀ClNO₄S requires: C, 50.1; H, 3.2; N, 4.5%; M, 311.5.

(b) Repetition of the reaction described in (a) before on a 0.01mol scale in anhydrous 1,2-dimethoxyethane (100ml) and with extension of the reaction time to 48h, followed by the same work up gave a beige semi- solid which was flash-chromatographed over silica.

Elution with hexane-dichloromethane (3:2) gave 1-(2-nitrothien-3-yl)-3-phenylpropane-1,3-dione (244) as a yellow solid (0.66g; 24%), mp 96-98°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

Further elution with hexane-dichloromethane (3:2) afforded 1-benzoyl-2-chloro-1-hydroxy-2-(2-nitrothien-3-yl)ethane (246) as a yellow solid (0.62g; 20%), which formed pale yellow microcrystals, mp 130-132°C (from ethanol), ν_{\max} 3364 br (OH), 1671 (C=O), and 1538 and 1396 (NO₂) cm⁻¹, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.18-8.10 (2H, m, ArH), 8.03 (1H, d, J 5.6, ArH), 7.75-7.66 (2H, m, ArH), 7.62-7.53 (2H, m, ArH), 6.66 (1H, d, J 8.3, OH)(exch.), 6.29 (1H, d, J 8.8, CH), and 5.58 (1H, t, J 8.5, CH).

Found: C, 50.0; H, 3.2; N, 4.5%; m/z(EIMS), 313, 311 (M⁺).

C₁₃H₁₀ClNO₄S requires: C, 50.1; H, 3.2; N, 4.5%; M, 311.5.

Final elution with hexane-dichloromethane (3:2) afforded 1-benzoyl-1-chloro-2-hydroxy-2-(2-nitrothien-3-yl)ethane (245) as a light brown solid (0.5g; 15%), mp 100-102°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

1-(2-Nitrothien-3-yl)-3-phenylpropane-1,3-dione Oxime (248)

A solution of the thienyl derivative (244) (0.55g; 0.002mol) in anhydrous ethanol (5.0ml) was stirred and treated with a solution of hydroxylamine hydrochloride (0.7g; 0.01mol) in anhydrous ethanol (25.0ml) added in one portion, followed by a single portion of anhydrous sodium carbonate (0.53g, 0.005mol). The resulting suspension was then stirred at room temperature with the exclusion of atmospheric moisture for 20h.

The red suspension was rotary evaporated and the residue was treated with water (5.0ml) and extracted several times with dichloromethane to afford the mono oxime derivative (248) as a brown solid (0.26g; 44%), which formed pale yellow microcrystals, mp 172-174°C (from ethanol), ν_{\max} 3224 (OH), 1714 (C=O), and 1549 and 1326 (NO₂) cm⁻¹, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 12.13 (1H, s, OH)(exch.), 8.01 (1H, d, J 5.4, ArH), 7.46 (5H, m, ArH), 7.18 (1H, d, J 5.4, ArH), and 4.61 (2H, s, CH₂)(exch.).

Found: C, 53.7; H, 3.4; N, 9.7%; m/z(EIMS), 290 (M⁺).

C₁₃H₁₀N₂O₄S requires: C, 53.8; H, 3.4; N, 9.7%; M, 290.

1-(2-Nitrothien-3-yl)-3-phenylpropane-1,3-dione Hydrazone (250)

A solution of the thienyl derivative (244) (0.55g; 0.002mol) in ethanol (5.0ml) was stirred and treated with a solution of hydrazine monohydrate (0.10g; 0.002mol) in ethanol (5.0ml) added in one portion. The mixture was then stirred and heated under reflux for 2h.

The dark red solution was rotary evaporated to give a viscous dark red oil which was flash- chromatographed over silica.

Elution with dichloromethane-ethyl acetate (7:3) gave a gummy red solid which was triturated with ether to afford the hydrazone derivative (250) as a red solid (0.18g; 30%), which formed red microcrystals, mp 160-162°C (from glacial acetic acid), ν_{\max} 3393 and 3280 (NH), and 1529 and 1378 (NO₂) cm⁻¹, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 7.83 (1H, d, J 5.5, ArH), 7.28-7.24 (3H, m, ArH), 7.15 (1H, s, NH)(exch.), 7.10 (2H, s, NH)(exch.),

7.04 (1H, s, NH)(exch.), 6.88-6.83 (2H, m, ArH), 6.44 (1H, d, J 5.5, ArH), and 4.17 (2H, s, CH₂).

Found: m/z(FABMS), 304.0865 [(M+H)⁺].

C₁₃H₁₃N₅O₂³²S requires: (M+H), 304.0868.

The Attempted Reaction of 1-(2-Nitrothien-3-yl)-3-phenylpropane-1,3-dione (244) with Benzenediazonium Chloride

A solution of redistilled aniline (0.20g; 0.0021mol) in 5M aqueous hydrochloric acid (1.0ml) was stirred and cooled to 0°C (ice- salt bath) then treated dropwise with stirring with a solution of sodium nitrite (0.15g; 0.0022mol) in water (0.5ml) at such a rate that the temperature was < 5°C. The resulting diazonium solution was stirred for a further 10min at 0-5°C after the addition was complete, then filtered through glass wool, and added dropwise with stirring at 0-5°C (ice- salt bath) to a solution of the thienyl diketone (244) (0.55g; 0.002mol) and anhydrous sodium acetate (0.41g; 0.005mol) in water (1.0ml) and ethanol (10.0ml). The mixture was then stirred in the melting ice bath for 2h.

The resulting dark red-purple suspension was filtered to afford the unreacted starting material (244) as a mustard-brown solid (0.37g; 68%), mp 97-99°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

Attempted Reduction Reactions of 1-(2-Nitrothien-3-yl)-3-phenylpropane-1,3-dione (244)

(a) A solution of the thienyl diketone (244) (0.55g; 0.002mol) in ethanol (30.0ml) was hydrogenated over 10% palladium-on-charcoal (0.06g) at room temperature and atmospheric pressure until no further hydrogen was absorbed.

The suspension was filtered through Celite and the pad was washed several times with warm ethanol and the combined ethanol extracts were rotary evaporated to give the unreacted starting material (244) as a red solid (0.5g; 91%), mp 92-95°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

- (b) A solution of the thienyl diketone (244) (0.55g; 0.002mol) in anhydrous dimethylformamide (10.0ml) was hydrogenated over Raney nickel (50% slurry in water)(0.11g; 0.055g Ni) at room temperature and atmospheric pressure until no further hydrogen was absorbed. Further Raney nickel (50% slurry in water)(0.11g; 0.055g Ni) was then added and hydrogenation continued at room temperature and atmospheric pressure until no further hydrogen was absorbed.

The mixture was filtered through Celite and the pad was washed several times with warm dimethylformamide. Rotary evaporation of the combined dimethylformamide extracts under high vacuum (oil pump) gave a viscous dark red oil (0.6g) from which no identifiable material could be obtained.

- (c) A solution of the thienyl diketone (244) (0.55g; 0.002mol) in tetrahydrofuran (20.0ml) was stirred and treated at room temperature with a solution of stannous chloride dihydrate (2.0g; 0.009mol) in 2M aqueous hydrochloric acid (20.0ml) added in one portion. The mixture was then stirred and heated under reflux for 1h.

The cooled solution was treated with 30% w/v aqueous sodium hydroxide solution (16.0ml) and was concentrated by rotary evaporation then extracted several times with dichloromethane to give a negligible amount of material.

The aqueous mother liquor was just acidified by the dropwise addition of concentrated hydrochloric acid then neutralised with solid anhydrous sodium acetate and extracted several times with dichloromethane but again gave only a negligible amount of material.

- (d) A solution of the thienyl diketone (244)(0.55g; 0.002mol) in 1,4-dioxane (8.0ml) was stirred and treated with 2% w/v aqueous sodium hydroxide solution (2.0ml) then 10% palladium on charcoal catalyst (0.008g). The mixture was stirred and purged with nitrogen for 15min then treated dropwise with stirring with a solution of sodium borohydride (0.15g; 0.004mol) in water (1.0ml). The mixture was then stirred at room temperature under nitrogen for 25min.

The purple suspension was filtered through Celite and the aqueous-dioxane filtrate was rotary evaporated under high vacuum (oil pump) and the residue was diluted with water (5.0ml) and was acidified with 2M aqueous hydrochloric acid then filtered to afford an intractable dark brown solid (0.4g) from which no identifiable material could be obtained.

The Attempted Oxidation of 1-(2-Nitrothien-3-yl)-3-phenylpropane-1,3-dione (244)

A solution of the thienyl diketone (244)(0.55g; 0.002mol) in 70% v/v aqueous glacial acetic acid (10.0ml) was stirred and treated at room temperature with small portions of solid chromium trioxide (1.1g). The mixture was then heated at 100°C for 0.5h.

The dark red solution was rotary evaporated under high vacuum (oil pump) and the residue was treated with water (5.0ml) then extracted several times with dichloromethane to give only a negligible amount of material.

The Attempted Base- catalysed Epimerisation of *Trans* 2-Benzoyl-3-(2-nitrothien-3-yl)oxirane (241)

A suspension of the *trans* oxirane (241) (0.55g; 0.002mol) in methanol (20.0ml) was stirred and treated at room temperature with a solution of sodium methoxide in methanol [0.4ml of a 10% w/v solution of sodium (0.5g) in methanol (4.5ml)]. The mixture was then stirred with the exclusion of atmospheric moisture at room temperature for 18h.

The dark red solution was made acidic by the dropwise addition of acetic acid then rotary evaporated at as low a temperature as possible and the residue was treated with water (5.0ml) and was extracted several times with dichloromethane. Rotary evaporation of the combined dichloromethane extracts gave an intractable dark red oil (0.22g) whose TLC in hexane-ethyl acetate (1:1) over silica showed it to be a multicomponent mixture which was not further investigated.

Epoxidation Reactions of 1,1-Diacyl-2-(2-nitrothien-3-yl)ethenes (236)

(a) A solution of the corresponding 1,1-diacyl-2-(2-nitrothien-3yl)ethene (236b) or (236c) (0.002mol) in Analar pyridine (5.0ml) was stirred and treated with

aqueous sodium hypochlorite solution (10-14% available chlorine; ca.2M)(5.0ml; 0.01mol) and the mixture then stirred at room temperature for 2h.

The mixture was treated with 2M aqueous hydrochloric acid (30.0ml) and extracted several times with dichloromethane to give a red oil which was triturated with ether to afford the unreacted oxirane derivatives (236b) or (236c) (63-67%), which were identified by comparison (mp and IR spectrum) with authentic samples.

- (b) A solution of the corresponding 1,1-diacyl-2-(2-nitrothien-3-yl)ethene (236) (0.002mol) in anhydrous 1,4-dioxane (10.0ml) was stirred and treated with aqueous sodium hypochlorite solution (14-15% available chlorine; ca.2M)(5.0ml; 0.01mol) and the mixture was then stirred at room temperature for 10min.

The resulting dark brown solution was concentrated by rotary evaporation and the residue diluted with water (5.0ml) and extracted several times with dichloromethane to give the crude product which was purified as described for the individual reactions below.

- (i) 3-Acetyl-4-(2-nitrothien-3-yl)but-3-en-2-one (236a) afforded only a dark red oil (0.25g) whose TLC in ethyl acetate over silica showed it to be largely baseline material and therefore was not further investigated.
- (ii) 3-Benzoyl-4-(2-nitrothien-3-yl)but-3-en-2-one (236b) afforded *cis* 2-benzoyl-3-(2-nitrothien-3-yl)oxirane (242) as a colourless solid (100%), which formed colourless microcrystals, mp 145-147°C (from ethanol), ν_{\max} 1686 (C=O), and 1544 and 1380 (NO₂) cm⁻¹, δ_{H} [(CD₃)₂SO] 7.90 (1H, d, J 1.5, ArH), 7.88 (1H, d, J 0.3, ArH), 7.76-7.71 (2H, m, ArH), 7.69-7.46 (2H, m, ArH), 7.03 (1H, dd, J 5.4 and 0.3, ArH), 5.20 (1H, d, J 5.1, CH), and 5.07 (1H, d, J 5.1, CH).

Found: C, 56.3; H, 3.4; N, 4.9%; m/z (HRFABMS), 276.0333 [(M+H)⁺].
C₁₃H₉NO₄³²S requires: C, 56.7; H, 3.3; N, 5.1%; (M+H), 276.0331.

(iii) 2-Benzoyl-3-(2-nitrothien-3-yl)-1-phenylprop-2-en-1-one (236c) afforded 2,2-dibenzoyl-3-(2-nitrothien-3-yl)oxirane (252c) as a colourless solid (86%), which formed colourless microcrystals, mp 150-152°C (from ethanol), ν_{\max} 1674 (C=O), and 1547 and 1371 (NO₂) cm⁻¹, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.09-8.04 (2H, m, ArH), 7.92-7.86 (3H, m, ArH), 7.75-7.44 (6H, m, ArH), 6.87 (1H, d, J 5.4, ArH), and 5.48 (1H, s, CH).

Found: C, 63.4; H, 3.2; N, 3.7%; m/z(FABMS), 382, 380 [(M+H)⁺].

C₂₀H₁₃NO₅S requires: C, 63.3; H, 3.4; N, 3.7%; M, 379.

(iv) The yellow oil obtained from E or Z ethyl 2-acetyl-3-(2-nitrothien-3-yl)prop-2-enoate (236d) was triturated with light petroleum to afford unreacted starting material (236d) as a yellow solid (67%), mp 40-43°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

The Reaction of *Cis* 2-Benzoyl-3-(2-nitrothien-3-yl)oxirane (242) with Hydrogen Chloride

A solution of the oxirane derivative (242) (0.63g; 0.002mol) in anhydrous 1,2-dimethoxyethane (20.0ml) was cooled to 0°C (ice-salt bath) and treated with a slow stream of hydrogen chloride until saturated. The resulting yellow suspension was then securely stoppered and stored in a fridge for 48h.

The resulting yellow-red solution was rotary evaporated and the yellow- brown semi-solid was triturated with ether to afford the 1-(2-nitrothien-3-yl)-3-phenylpropane-1,3-dione (244) as a yellow- brown solid (1.8g; 84%), mp 98-100°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

The Attempted Reaction of 2,2-Dibenzoyl-3-(2-nitrothien-3-yl)oxirane (252c) with Hydrogen Chloride

A solution of the oxirane derivative (252c) (0.76g; 0.002mol) in anhydrous 1,2-dimethoxyethane (20.0ml) was cooled to 0°C (ice-salt bath) and treated with a slow stream of hydrogen chloride until saturated. The yellow solution was then securely stoppered and stored in a fridge for 64h.

The resulting orange suspension was filtered to afford the unreacted starting material (252c) as a yellow solid (0.25g; 33%), mp 149-151°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

Rotary evaporation of the 1,2-dimethoxyethane mother liquor gave a brown oil which was treated with 10% w/v aqueous sodium hydrogen carbonate solution (2.5ml) then extracted several times with dichloromethane to give a brown oil which was triturated with ether to afford only a second crop of unreacted starting material (252c) as a yellow solid (0.09g; 12%), mp 150-152°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

Attempted Reactions of *Trans* 2-Benzoyl-3-(2-nitrothien-3-yl)oxirane (241) with Stannic Chloride

- (a) A solution of the oxirane derivative (241) (0.55g; 0.002mol) in anhydrous toluene (15.0ml) was stirred and treated dropwise at room temperature with a solution of stannic chloride (0.56g; 0.0022mol) in anhydrous toluene (5.0ml). The mixture was then stirred at room temperature with the exclusion of atmospheric moisture for 15min.

The resulting dark brown suspension was poured on to ice (40g) and the aqueous layer separated and extracted several times with dichloromethane. Rotary evaporation of the combined toluene and dichloromethane extracts gave a dark red oil flash- chromatography of which yielded no identifiable material.

- (b) Repetition of the reaction described in (a) before but in anhydrous dichloromethane as solvent afforded after work up, a dark red intractable oil whose TLC in hexane-dichloromethane (1:2) over silica showed it to be a multicomponent mixture which therefore was not further investigated.
- (c) Repetition of the reaction described in (b) before but at 0°C gave a viscous intractable oil whose TLC in hexane-dichloromethane (1:2) over silica showed it to be a multicomponent mixture which therefore was not further investigated.

Reactions of *Trans* 2-Benzoyl-3-(2-nitrothien-3-yl)oxirane (241) with Boron Trifluoride Etherate

- (a) A solution of the oxirane derivative (241) (0.55g; 0.002mol) in anhydrous 1,2-dimethoxyethane (15.0ml) was stirred and treated dropwise at room temperature with a solution of boron trifluoride etherate (1.2g; 1.0ml; 0.008mol) in anhydrous 1,2-dimethoxyethane (5.0ml) and the mixture was then stirred at room temperature with the exclusion of atmospheric moisture for 15min.

The resulting yellow solution was poured carefully on to ice (20g) and stirred briefly then extracted several times with dichloromethane to give a semi-solid which was triturated with ether to afford unreacted starting material (241) as a light brown solid (0.46g; 84%), mp 144-146°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

- (b) Repetition of the reaction described in (a) before but under reflux for 15min followed by the same work up gave a dark red oil which was flash-chromatographed over silica eluting with hexane-dichloromethane (2:3) to give 2-(1,2-dioxo-2-phenyl)ethylaminothiophene-3-carboxylic acid (254) as an orange solid (0.12g; 22%), which formed orange microcrystals, mp 105-107°C (from ethyl acetate- light petroleum), ν_{\max} 3400-2000 br (OH), and 1683 (C=O) cm^{-1} , $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 12.10 (1H, br s, OH or NH)(exch.), 7.96 (1H, d, J 5.5, ArH), 7.61-7.47 (5H, m, ArH), 7.26 (1H, d, J 5.5, ArH), and 3.80 (1H, br s, OH or NH)(exch.).

Found: C, 56.5; H, 3.4; N, 5.0%; m/z (HREIMS), 275.0253 (M^+).

$\text{C}_{13}\text{H}_9\text{NO}_4^{32}\text{S}$ requires: C, 56.7; H, 3.3; N, 5.1%; M, 275.0252.

- (c) Repetition of the reaction described in (b) before but at 50°C for 19h followed by the same work up gave a red-brown oil which was flash- chromatographed over silica eluting with hexane-dichloromethane (2:3) to afford 2-(1,2-dioxo-2-phenyl)ethylaminothiophene-3-carboxylic acid (254) as an orange solid (0.25g; 45%), mp 104-106°C, identified by comparison (mp and IR spectrum) with a sample obtained in (b) before.

The Attempted Reaction of 2-(1,2-Dioxo-2-phenyl)ethylaminothiophene-3-carboxylic Acid (254) with Acetic Anhydride

The thiophene carboxylic acid derivative (254) (0.55g; 0.002mol) was treated with acetic anhydride (5.0ml) and the mixture stirred and heated under reflux with the exclusion of atmospheric moisture for 3h.

The dark brown solution obtained was rotary evaporated under high vacuum (oil pump) to give a dark brown- black oil (0.6g) flash- chromatography of which over silica gave only a series of intractable oils and gums which yielded no identifiable material.

N,N'-Diethyloxamide (260)

N,N'-Diethyloxamide (260) was prepared by the reaction of diethyl oxalate (259) with aqueous ethylamine as described by Wallach, as a colourless solid (79%), mp 178-180°C (Lit.,⁹⁵ 175°C) and was used without further purification.

5-Chloro-1-ethyl-2-methyl-1H-imidazole (261)

5-Chloro-1-ethyl-2-methyl-1H-imidazole (261) was prepared by the reaction of N,N'-diethyloxamide (260) with phosphorus pentachloride as described by Wallach, as a colourless oil (75%), bp 75°C/0.4mmHg (Lit.,⁹⁶ 76-78°C/0.09mmHg) and was used without further purification.

5-Chloro-1-ethyl-2-methyl-4-nitro-1H-imidazole (262)

5-Chloro-1-ethyl-2-methyl-4-nitro-1H-imidazole (262) was prepared by the nitration of 5-chloro-1-ethyl-2-methyl-1H-imidazole (261) as described by Sarasin and Wegmann, as a cream solid (71%), mp 88-90°C (Lit.,⁹⁷ 88°C) and was used without further purification.

Diethyl 2-(1-Ethyl-2-methyl-4-nitro-1H-imidazole-5-yl)propane-1,3-dioate (263)

The nitroimidazole diester (263) was prepared by the sodium hydride promoted reaction of 5-chloro-1-ethyl-2-methyl-4-nitro-imidazole (262) with diethyl propane-1,3-dioate in dimethylformamide as described by Tennant, Wallis, and Weaver, as a

light brown solid (82%), mp 96-98°C (Lit.,⁹³ 98-99°C) and was used without further purification.

1-Ethyl-2,5-dimethyl-4-nitro-1H-imidazole (256)

A suspension of the nitroimidazole diester (263) (21.9g; 0.07mol) in 10% w/v aqueous hydrochloric acid (175.0ml) was stirred and heated under reflux for 4h.

The mixture was cooled (ice bath) and treated dropwise with stirring with 20% w/v aqueous sodium hydroxide solution until just alkaline and then with glacial acetic acid to obtain a pH of 6-7. Extraction several times with dichloromethane afforded the nitroimidazole derivative (256) as a pink coloured solid (9.3g; 78%), which formed pink microcrystals, mp 84-86°C (from light petroleum)(lit.,⁹⁴ 85-86°C), ν_{\max} 1543 and 1377 (NO₂) cm⁻¹, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 3.99 (2H, q, J 7.3, CH₂), 2.56 (3H, s, CH₃), 2.35 (3H, s, CH₃), and 1.23 (3H, t, J 7.3, CH₃).

Found: C, 49.6; H, 6.6; N, 24.7%; m/z(EIMS), 169 (M⁺).

C₇H₁₁N₃O₂ requires: C, 49.7; H, 6.5; N, 24.9%; M, 169.

1-(N,N-Dimethylamino)-2-(1-ethyl-2-methyl-4-nitro-1H-imidazol-5-yl)ethene (257)

A solution of the nitroimidazole derivative (256) (3.4g; 0.02mol) in anhydrous dimethylformamide (20.0ml) was treated with a solution of N,N-dimethylformamide dimethyl acetal (4.8g; 0.04mol) in anhydrous dimethylformamide (20.0ml) and the mixture stirred and heated under reflux with the exclusion of atmospheric moisture for 18h.

The red solution was rotary evaporated under high vacuum (oil pump) to give a dark red oil (4.5g) which was triturated with ether to afford the enamine (257) as a red solid (4.4g; 98%), which formed red microcrystals, mp 94-96°C (from ethyl acetate-light petroleum), ν_{\max} 1527 and 1372 (NO₂) cm⁻¹, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 7.99 (1H, d, J 13.2, CH), 5.10 (1H, d, J 13.2, CH), 3.96 (2H, q, J 7.2, CH₂), 2.96 (6H, s, 2 x CH₃), 2.30 (3H, s, CH₃), and 1.23 (3H, t, J 7.2, CH₃).

Found: C, 53.2; H, 7.2; N, 24.6%; m/z(HREIMS), 224.1274 (M^+).
C₁₀H₁₆N₄O₂ requires: C, 53.6; H, 7.1; N, 25.0%; M, 224.1273.

1-Ethyl-2-methyl-4-nitro-1H-imidazole-5-carboxaldehyde (258)

A suspension of the nitroimidazole enamine (257) (2.2g; 0.01mol) in tetrahydrofuran (50.0ml) was stirred and treated with a solution of sodium periodate (6.4g; 0.03mol) in water (50.0ml) added in one portion. The mixture was then stirred at room temperature for 1h.

The mixture was filtered and the inorganic filter cake washed several times with ethyl acetate. The aqueous filtrate was separated and washed several times with ethyl acetate. The combined ethyl acetate extracts were washed with 10% w/v aqueous sodium hydrogen carbonate solution (3 x 20.0ml) and rotary evaporated to give the nitroimidazole carboxaldehyde (258) as a red oil (1.8g; 100%), bp 210°C/0.2mmHg, ν_{\max} 1685 (C=O), and 1546 and 1333 (NO₂) cm⁻¹, $\delta_H[(CD_3)_2SO]$ 10.21 (1H, s, CH), 4.30 (2H, q, J 7.2, CH₂), 2.47 (3H, s, CH₃), and 1.27 (3H, t, J 7.2, CH₃).

Found: C, 45.6; H, 5.1; N, 22.8%; m/z(EIMS), 183 (M^+).
C₇H₉N₃O₃ requires: C, 45.9; H, 4.9; N, 23.0%; M, 183.

The Attempted Reaction of 1-Ethyl-2-methyl-4-nitro-1H-imidazole-5-carboxaldehyde (258) with Pentane-2,4-dione (136a) in the Presence of Hydrogen Chloride

A solution of the nitroimidazole carboxaldehyde (258) (0.9g; 0.005mol) in anhydrous ether (45.0ml) was stirred and treated with a solution of pentane-2,4-dione (136a) (0.5g; 0.005mol) in anhydrous ether (5.0ml), and the mixture was cooled to 0°C (ice- salt bath) and treated with a slow stream of hydrogen chloride until saturated. The mixture was then securely stoppered and stored in a fridge for 19h.

The resulting suspension was filtered to afford a deliquescent solid which was treated with water (2.0ml) and the resulting mixture extracted several times with dichloromethane to afford the unreacted nitroimidazole carboxaldehyde (258) as an

orange liquid (0.35g; 39%), which was identified by comparison (IR spectrum and TLC in dichloromethane over silica) with a sample obtained before.

Rotary evaporation of the ethereal mother liquor gave an amber oil (0.2g) whose TLC in dichloromethane over silica showed it to be only a mixture of the two starting materials and therefore was not further investigated.

3-Acetyl-4-(1-ethyl-2-methyl-4-nitro-1H-imidazol-5-yl)but-3-en-2-one (264)

(a) 1-Ethyl-2-methyl-4-nitro-1H-imidazole-5-carboxaldehyde (258) (0.96g; 0.005mol) and pentane-2,4-dione (136a) (0.6g; 0.0066mol) were mixed with glacial acetic acid (0.4g; 0.4ml; 0.0066mol) and the mixture was stirred and treated at room temperature with piperidine (0.43g; 0.5ml; 0.005mol). The mixture was then stirred at room temperature with the exclusion of atmospheric moisture for 2h.

The resulting red solution was rotary evaporated to give a red oil which was flash- chromatographed over silica.

Elution with hexane-dichloromethane (3:7) gave crude unreacted nitroimidazole carboxaldehyde (258) as a brown oil (20%), identified by comparison (IR spectrum and TLC in dichloromethane over silica) with a sample obtained before.

Further elution with dichloromethane afforded 3-acetyl-4-(1-ethyl-2-methyl-4-nitro-1H-imidazol-5-yl)but-3-en-2-one (264) as a yellow solid (23%), which formed yellow microcrystals, mp 107-109°C (from ethanol), ν_{\max} 1704 (C=O), and 1532 and 1375 (NO₂) cm⁻¹, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 7.63 (1H, s, CH), 4.02 (2H, q, J 7.2, CH₂), 2.54 (3H, s, CH₃), 2.42 (3H, s, CH₃), 2.14 (3H, s, CH₃), and 1.23 (3H, t, J 7.2, CH₃).

Found: C, 54.4; H, 5.6; N, 15.5%; m/z(FABMS), 266 [(M+H)⁺].

C₁₂H₁₅N₃O₄ requires: C, 54.3; H, 5.7; N, 15.8%; M, 265.

- (b) Solutions of the nitroimidazolecarboxaldehyde (258) (0.96g; 0.005mol) and pentane-2,4-dione (136a) (0.6g; 0.006mol) in anhydrous ethanol (12.5ml) and glacial acetic acid (0.4g; 0.4ml; 0.0066mol) in anhydrous ethanol (5.0ml) were mixed, stirred, and treated at room temperature with a solution of piperidine (0.43g; 0.5ml; 0.005mol) in anhydrous ethanol (2.5ml). The mixture was then stirred at room temperature with the exclusion of atmospheric moisture for 2h.

The resulting red solution was rotary evaporated to give a red oil which was flash- chromatographed over silica.

Elution with dichloromethane gave unreacted nitroimidazole carboxaldehyde (258) as a brown oil (68%) which was identified by comparison (IR spectrum and TLC in dichloromethane over silica) with a sample obtained before.

Further elution with dichloromethane afforded the nitroimidazolylethene (264) as a yellow solid (15%), mp 99-102°C, identified by comparison (mp and IR spectrum) with an authentic sample obtained before.

- (c) Repetition of the reaction described in (b) before but under reflux followed by the same work up gave a red oil which was flash- chromatographed over silica.

Elution with dichloromethane gave unreacted nitroimidazolecarboxaldehyde (258) as a red oil (19%), identified by comparison (IR spectrum and TLC in dichloromethane over silica) with an authentic sample obtained before.

Further elution with dichloromethane-ethyl acetate (9:1) afforded the alkene (264) as a yellow solid (57%), mp 99-102°C, identified by comparison (mp and IR spectrum) with an authentic sample obtained before.

- (d) Repetition of the reaction described in (c) before but with extension of the reaction time to 4h followed by the same work up and flash- chromatography of the red oil obtained over silica afforded unreacted nitroimidazolecarboxaldehyde (258) (16%), identified by comparison (IR spectrum and TLC in dichloromethane over silica) with an authentic sample obtained before, and 3-acetyl-4-(1-ethyl-2-methyl-4-nitro-1H-imidazol-5-yl)but-3-en-2-one (264) (38%), mp 103-106°C,

which was identified by comparison (mp and IR spectrum) with a sample obtained before.

Attempted Reactions of 3-Acetyl-4-(1-ethyl-2-methyl-4-nitro-1H-imidazol-5-yl)but-3-en-2-one (264) with Hydrogen Chloride

- (a) A solution of the alkene (264) (0.53g; 0.002mol) in anhydrous 1,2-dimethoxyethane (20.0ml) was stirred and cooled to 0°C (ice- salt bath) and treated with a slow stream of hydrogen chloride until saturated. The yellow solution then was securely stoppered and left in a fridge for 24h.

The resulting orange- yellow solution was rotary evaporated and the amber oil was treated with 10% w/v aqueous sodium hydrogen carbonate solution (5.0ml) and extracted several times with dichloromethane. Rotary evaporation of the combined dichloromethane extracts gave a gummy red solid which was triturated with ether to afford the unreacted alkene (264) as an orange- red solid (70%), mp 102-105°C, which was identified by comparison (mp and IR spectrum) with a sample obtained before.

- (b) Repetition of the reaction described in (a) before but with extension of the reaction time to 96h followed by the same work up afforded only the unreacted alkene (264) as an orange solid (75%), mp 100-103°C, which was identified by comparison (mp and IR spectrum) with an authentic sample.

Trans 2-Benzoyl-3-(1-ethyl-2-methyl-4-nitro-1H-imidazol-5-yl)oxirane (266)

A suspension of the nitroimidazole carboxaldehyde (258) (3.6g; 0.02mol) and 2-bromoacetophenone (4.0g; 0.02mol) in methanol (60.0ml) was stirred and cooled to 0-10°C (ice bath) then treated dropwise with a solution of sodium (0.48g; 0.02g. atom) in methanol (20.0ml). The mixture was then stirred at room temperature with the exclusion of atmospheric moisture for 3h.

The suspension was acidified to pH 6 by the addition of glacial acetic acid and then filtered to afford the *trans* oxirane derivative (266) as a cream solid (4.8g; 80%), which formed cream microcrystals, mp 144-146°C (from ethanol), ν_{\max} 1682 (C=O), and 1531 and 1379 (NO₂) cm⁻¹, δ_{H} [(CD₃)₂SO] 8.16-8.11 (2H, m, ArH), 7.77-7.71

(1H, m, ArH), 7.62-7.56 (2H, m, ArH), 5.09 (1H, d, J 2.0, CH), 4.55 (1H, d, J 2.0, CH), 4.14 (2H, q, J 7.2, CH₂), 2.41 (3H, s, CH₃), and 1.35 (3H, t, J 7.2, CH₃).

Found: C, 59.5; H, 5.1; N, 13.9%; m/z(FABMS), 302 [(M+H)⁺].

C₁₅H₁₅N₃O₄ requires: C, 59.8; H, 5.0; N, 14.0%; M, 301.

Reactions of *Trans* 2-Benzoyl-3-(1-ethyl-2-methyl-4-nitro-1H-imidazol-5-yl)oxirane (266) with Hydrogen Chloride

- (a) A solution of the oxirane derivative (266) (1.1g; 0.004mol) in anhydrous 1,4-dioxane (40.0ml) was stirred and cooled to 11°C (ice- water bath) then treated with a slow stream of hydrogen chloride until saturated. The mixture was then securely stoppered and stored in a fridge for 24h.

The resulting suspension was filtered and the solid was treated with 10% w/v aqueous sodium hydrogen carbonate solution (10.0ml) and extracted several times with dichloromethane to give only an intractable yellow oil (0.7g), which yielded no identifiable material.

Rotary evaporation of the 1,4-dioxane filtrate gave a red liquid which was treated with 10% w/v aqueous sodium hydrogen carbonate solution (5.0ml) and extracted several times with dichloromethane to give only a red oil (0.3g), which yielded no identifiable material.

- (b) Repetition of the reaction described in (a) before but in 1,2-dimethoxyethane as solvent followed by the same work up gave a viscous orange- red oil which was triturated with ether-ethyl acetate to afford the unreacted oxirane derivative (266) as a pale yellow solid (0.8g; 73%), mp 138-141°C, which was identified by comparison (mp and IR spectrum) with a sample obtained before.
- (c) Repetition of the reaction described in (b) before but with extension of the reaction time to 96h followed by the same work up gave an amber oil which was flash- chromatographed over silica.

Elution with ether-dichloromethane (1:9) afforded 1-benzoyl-2-chloro-1-hydroxy-2-(1-ethyl-2-methyl-4-nitro-1H-imidazol-5-yl)ethane (268) as a colourless solid (0.25g; 18%), which formed colourless microcrystals, mp 151-153°C (from ethanol-light petroleum), ν_{\max} 3458 (OH), 1676 (C=O), and 1536 and 1349 (NO₂) cm⁻¹, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 7.95 (1H, d, J 1.1, ArH), 7.91 (1H, d, J 1.5, ArH), 7.70-7.49 (3H, m, ArH), 6.88 (1H, d, J 7.8, OH)(exch.), 6.07 (1H, d, J 6.6, CH), 5.84 (1H, dd, J 7.4 and 7.3, CH), 4.49-4.16 (2H, m, CH₂), 2.37 (3H, s, CH₃), and 1.32 (3H, t, J 7.2, CH₃), $\delta_{\text{C}}[(\text{CD}_3)_2\text{SO}]$ 197.6 (quat.), 145.1 (quat.), 142.3 (quat.), 134.5 (quat.), 134.0 (CH), 128.9 (2 x CH), 128.7 (2 x CH), 128.4 (quat.), 73.8 (CH), 53.8 (CH), 40.9 (CH₂), 15.0 (CH₃), and 13.1 (CH₃).

Found: C, 53.0; H, 4.9; N, 12.3%; m/z(FABMS), 340, 338 [(M+H)⁺].
C₁₅H₁₆ClN₃O₄ requires: C, 53.3; H, 4.7; N, 12.4%; M, 337.5.

Further elution with ether-dichloromethane (1:9) gave 1-phenyl-3-(1-ethyl-2-methyl-4-nitro-1H-imidazol-5-yl)propane-1,2-dione (269) as a pale yellow solid (0.12g; 10%), which formed pale yellow microcrystals, mp 160-162°C (from ethanol), ν_{\max} 1724 and 1673 (C=O), and 1576 and 1334 (NO₂) cm⁻¹, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.01-7.96 (2H, m, ArH), 7.75-7.71 (1H, m, ArH), 7.63-7.55 (2H, m, ArH), 4.84 (2H, s, CH₂), 4.09 (2H, q, J 7.2, CH₂), 2.48 (3H, s, CH₃), and 1.24 (3H, t, J 7.2, CH₃), $\delta_{\text{C}}[(\text{CD}_3)_2\text{SO}]$ 195.7 (quat.), 189.4 (quat.), 144.1 (quat.), 143.7 (quat.), 134.9 (CH), 131.7 (quat.), 130.4 (2 x CH), 129.0 (2 x CH), 128.2 (quat.), 39.4 (CH₂), 34.9 (CH₂), 15.3 (CH₃), and 13.0 (CH₃).

Found: C, 59.9; H, 5.0; N, 14.0%; m/z(EIMS), 301 (M⁺).
C₁₅H₁₅N₃O₄ requires: C, 59.8; H, 5.0; N, 14.0%; M, 301.

The Reaction of 1-Benzoyl-2-chloro-1-hydroxy-2-(1-ethyl-2-methyl-4-nitro-1H-imidazol-5-yl)ethane (268) with Acetic Anhydride

The chlorohydrin derivative (268) (0.6g; 0.002mol) was treated with acetic anhydride (5.0ml) and heated under reflux with the exclusion of atmospheric moisture for 3h.

The resulting red solution was rotary evaporated under high vacuum (oil pump) to give a red oil which was flash- chromatographed over silica.

Elution with dichloromethane-ethyl acetate (4:1) gave a yellow oil which was triturated with ether to afford 1-acetoxy-1-benzoyl-2-chloro-2-(1-ethyl-2-methyl-4-nitro-1H-imidazol-5-yl)ethane (274) as a colourless solid (0.09g; 12%), which formed colourless microcrystals, mp 146-148°C (from ethyl acetate-light petroleum), ν_{\max} 1759 and 1705 (C=O), and 1549 and 1384 (NO₂) cm⁻¹, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 8.17-8.13 (1H, m, ArH), 7.84-7.79 (2H, m, ArH), 7.68-7.64 (1H, m, ArH), 7.56-7.49 (2H, m, ArH), 6.84 (1H, d, J 7.5, CH), 6.28 (1H, d, J 7.5, CH), 4.47-4.05 (2H, m, CH₂), 2.30 (3H, s, CH₃), 2.20 (3H, s, CH₃), and 1.29 (3H, t, J 7.0, CH₃).

Found: C, 53.7; H, 4.9; N, 11.2%; m/z(FABMS), 382, 380 [(M+H)⁺].

C₁₇H₁₈ClN₃O₅ requires: C, 53.8; H, 4.7; N, 11.1%; M, 379.5.

Further elution with dichloromethane-ethyl acetate (4:1) gave an amber oil which was triturated with ether to afford 1-acetoxy-1-benzoyl-2-(1-ethyl-2-methyl-4-nitro-1H-imidazol-5-yl)ethene (275) as a colourless solid (0.3g; 44%), mp 148-150°C (from ethyl acetate), ν_{\max} 1757 and 1701 (C=O), 1593 and 1340 (NO₂) cm⁻¹, $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 7.94-7.93 (2H, m, ArH), 7.74-7.56 (3H, m, ArH), 6.98 (1H, s, CH), 4.02 (2H, q, J 7.0, CH₂), 2.43 (3H, s, CH₃), 2.06 (3H, s, CH₃), and 1.20 (3H, t, J 7.2, CH₃), $\delta_{\text{C}}[(\text{CD}_3)_2\text{SO}]$ 188.5 (quat.), 167.6 (quat.), 148.1 (quat.), 145.3 (quat.), 135.2 (2 x quat.), 133.7 (CH), 129.4 (2 x CH), 128.9 (2 x CH), 123.0 (quat.), 112.2 (CH), 40.1 (CH₂), 19.9 (CH₃), 14.8 (CH₃), and 12.9 (CH₂).

Found: C, 58.8; H, 5.0; N, 12.0%; m/z(HREIMS), 343.1172 (M⁺).

C₁₇H₁₇N₃O₅ requires: C, 59.5; H, 5.0; N, 12.2%; M, 343.1168.

The Attempted Catalytic Hydrogenation of 1-Benzoyl-2-chloro-1-hydroxy-2-(1-ethyl-2-methyl-4-nitro-1H-imidazol-5-yl)ethane (268)

The chlorohydrin (268) (0.34g; 0.001mol) was hydrogenated in anhydrous 1,2-dimethoxyethane (10.0ml) over palladium-on-charcoal catalyst (0.03g) at room temperature and atmospheric pressure until no further hydrogen was absorbed.

The suspension was filtered through Celite and the pad was washed with warm anhydrous 1,2-dimethoxyethane. Rotary evaporation of the combined ethanol filtrate and washings gave a gummy red solid which was triturated with ether to afford the unreacted chlorohydrin (268) as a pink solid (0.27g; 79%), mp 147-150°C, which was identified by comparison (mp and IR spectrum) with a sample obtained before.

The Attempted Oxidation Reactions of 1-Benzoyl-2-chloro-1-hydroxy-2-(1-ethyl-2-methyl-4-nitro-1H-imidazol-5-yl)ethane (268) Using Manganese Dioxide in 1,2-Dimethoxyethane

(a) A solution of the chlorohydrin derivative (268) (0.002mol) in anhydrous 1,2-dimethoxyethane (10.0ml) was stirred and treated at room temperature with activated manganese dioxide (Aldrich 21,764-6)(1.0g) added in one portion. The mixture was then stirred at room temperature with the exclusion of atmospheric moisture for 0.5h.

The resulting suspension was filtered through Celite and the filter pad washed several times with anhydrous 1,2-dimethoxyethane. Rotary evaporation of the combined filtrate and washings under high vacuum (oil pump) gave the unreacted chlorohydrin derivative (268) as an orange solid (91%), mp 145-148°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

(b) Repetition of the reaction described in (a) before but under reflux followed by the same work up gave a red oil which was flash- chromatographed over silica.

Elution with dichloromethane-ethyl acetate (9:1) gave a viscous yellow-orange oil which was triturated with ether to afford the unreacted chlorohydrin derivative (268) as a yellow solid (24%), mp 145-148°C, identified by comparison (mp and IR spectrum) with a sample obtained before.

The Attempted Reaction of 1-Benzoyl-2-chloro-1-hydroxy-2-(1-ethyl-2-methyl-4-nitro-1H-imidazol-5-yl)ethane (268) with 2M Aqueous Sodium Hydroxide Solution

The chlorohydrin derivative (268) (0.3g; 0.001mol) was treated with 2M sodium hydroxide solution (1.0ml) and gently warmed until all of the solid was in solution.

The resulting red solution was allowed to cool to room temperature and was just acidified with 2M hydrochloric acid and then brought to pH 7 by the addition of solid anhydrous sodium acetate. The orange-red solution was extracted several times with dichloromethane to yield no identifiable material.

Attempted Reactions of 3-Acetyl-4-(1-ethyl-2-methyl-4-nitro-1H-imidazol-5-yl)but-3-en-2-one (264) with Aqueous Sodium Hypochlorite

(a) A solution of the alkene (264) (0.53g; 0.002mol) in 1,4-dioxane (10.0ml) was stirred and treated at room temperature with aqueous sodium hypochlorite solution (14-15% available chlorine; ca.2M)(5.0ml; 0.01mol). The mixture was then stirred at room temperature for 10min.

The orange-brown solution as rotary evaporated at as low a temperature as possible and the residue was treated with water (5.0ml) and extracted several times with dichloromethane to give a dark red intractable oil (0.17g) whose TLC in dichloromethane-ethyl acetate (1:1) over silica showed it to be largely baseline material.

Neutralisation of the aqueous mother liquor with aqueous hydrochloric acid and solid sodium acetate and extraction several times with dichloromethane afforded no other identifiable material.

(b) A solution of the alkene (264) (0.53g; 0.002mol) in Analar pyridine (5.0ml) was stirred and treated with aqueous sodium hypochlorite solution (14-15% available chlorine; ca.2M)(5.0ml; 0.01mol), and the mixture was then stirred at room temperature for 10min.

The dark red mixture was treated with 2M aqueous hydrochloric acid (30.0ml) then extracted several times with dichloromethane to give only a red intractable

oil (0.3g) whose TLC in dichloromethane-ethyl acetate (1:2) over silica showed it to be largely baseline material.

Reactions of *Trans* 2-Benzoyl-3-(1-ethyl-2-methyl-4-nitro-1H-imidazol-5-yl)oxirane (266) with Stannic Chloride

- (a) A solution of the oxirane derivative (266) (0.6g; 0.002mol) in anhydrous toluene (15.0ml) was stirred and treated dropwise at room temperature with a solution of stannic chloride (0.56g; 0.0022mol) in anhydrous toluene (5.0ml). The mixture was then stirred at room temperature with the exclusion of atmospheric moisture for 15min.

The resulting red-orange suspension was poured on to ice (40g) and the toluene layer was separated. The aqueous mother liquor was extracted several times with dichloromethane, and the combined dichloromethane-toluene extracts rotary evaporated to give a gummy yellow solid which was triturated with ether to afford the chlorohydrin derivative (268) as a colourless solid (0.4g; 59%), mp 152-154°C, which was identified by comparison (mp and IR and ¹H NMR spectra) with a sample obtained before.

- (b) Repetition of the reaction described in (a) before, but in dichloromethane followed by the same work up gave a yellow foam which was triturated with ether to afford the chlorohydrin derivative (268) as a colourless solid (0.64g; 95%), mp 151-153°C, which was identified by comparison (mp and IR spectrum) with an authentic sample obtained before.

Reaction of *Trans* 2-Benzoyl-3-(1-ethyl-2-methyl-4-nitro-1H-imidazol-5-yl)oxirane (266) with Boron Trifluoride Etherate in 1,2-Dimethoxyethane

A solution of the oxirane derivative (266) (1.5g; 0.005mol) in anhydrous 1,2-dimethoxyethane (30.0ml) was stirred and treated dropwise at room temperature with a solution of boron trifluoride etherate (3.0g; 2.5ml; 0.02mol) in anhydrous 1,2-dimethoxyethane (20.0ml). After the addition was complete the mixture was stirred and heated under reflux with the exclusion of atmospheric moisture for 15min.

The resulting orange-red solution was poured carefully on to ice (50g) and the mixture extracted several times with dichloromethane to give an orange foam which was triturated with ethanol-ether to afford 1-ethyl-2-methyl-4-(1,2-dioxo-2-phenyl)ethylamino-1H-imidazole-5-carboxylic acid (279) as a light brown solid (0.7g; 47%), which formed pale yellow microcrystals, mp 210-212°C (from ethanol-light petroleum), ν_{\max} 3600-2250 br (OH and NH), and 1639 (C=O) cm^{-1} , $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 7.81 (1H, s, ArH), 7.66-7.48 (4H, m, ArH), 3.87 (2H, q, J 7.2, CH_2), 2.44 (3H, s, CH_3), and 1.06 (3H, t, J 7.0, CH_3), $\delta_{\text{C}}[(\text{CD}_3)_2\text{SO}]$ 192.4 (quat.), 166.3 (quat.), 144.2 (quat.), 143.4 (quat.), 139.0 (quat.), 131.6 (CH), 128.7 (2 x CH), 128.6 (2 x CH), 127.5 (quat.), 108.1 (quat.), 40.0 (CH_2), 15.1 (CH_3), and 13.2 (CH_3).

Found: C, 59.7; H, 5.3; N, 13.8%; m/z (FABMS), 302 $[(\text{M}+\text{H})^+]$.

$\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}_4$ requires: C, 59.8; H, 5.0; N, 14.0%; M, 301.

Rotary evaporation of the ethanol-ether filtrate gave a red oil which was flash-chromatographed over silica.

Elution with dichloromethane-ethyl acetate (4:1) gave *E* or *Z* 1-benzoyl-2-methoxy-2-(1-ethyl-2-methyl-4-nitro-1H-imidazol-5-yl)ethene (278) as a light brown solid (0.2g; 13%), which formed colourless microcrystals, mp 168-170°C (from ethanol), ν_{\max} 1631 (C=O), and 1532 and 1378 (NO_2) cm^{-1} , $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 7.74-7.69 (2H, m, ArH), 7.62-7.52 (3H, m, ArH), 3.92 (1H, s, CH), 3.87 (2H, q, J 7.3, CH_2), 3.36 (3H, s, CH_3), 2.44 (3H, s, CH_3), and 1.20 (3H, t, J 7.2, CH_3).

Found: C, 61.0; H, 5.6; N, 13.2%; m/z (FABMS), 316 $[(\text{M}+\text{H})^+]$.

$\text{C}_{16}\text{H}_{17}\text{N}_3\text{O}_4$ requires: C, 61.0; H, 5.4; N, 13.3%; M, 315.

The Reaction of 1-ethyl-2-methyl-4-(1,2-dioxo-2-phenyl)ethylamino-1H-imidazole-5-carboxylic acid (279) with Acetic Anhydride

The imidazole carboxylic acid derivative (279) (0.3g; 0.001mol) was treated with acetic anhydride (2.5ml) and heated under reflux for 3h.

The resulting dark brown solution was rotary evaporated under high vacuum (oil pump) and gave a dark red oil which was flash- chromatographed over silica.

Elution with dichloromethane-ethyl acetate (9:1) gave a red oil which was triturated with ether-ethyl acetate to give 5-benzoyl-1-ethyl-2-methyl-7-oxo-1H,7H-imidazo[5,4-d]-1,3-oxazine (280) (0.03g, 9%) as a light brown solid, mp 157-159°C, ν_{\max} 1743, 1696 and 1670 (C=O) cm^{-1} .

Found: C, 62.6; H, 4.7; N, 13.9%; m/z (HREIMS), 283.0961 (M^+).

$C_{15}H_{13}N_3O_3$ requires: C, 63.6; H, 4.6; N, 14.8%; M, 283.0957.

Further elution with dichloromethane-ethyl acetate (9:1) yielded no other identifiable material.

Reaction of 1-Benzoyl-2-chloro-1-hydroxy-2-(1-ethyl-2-methyl-4-nitro-1H-imidazol-5-yl)ethane (268) with Boron Trifluoride Etherate in 1,2-Dimethoxyethane

A solution of the chlorohydrin derivative (268) (0.6g; 0.002mol) in anhydrous 1,2-dimethoxyethane (10.0ml) was stirred and treated dropwise at room temperature with a solution of boron trifluoride etherate (1.2g; 1.0ml; 0.008mol) in anhydrous 1,2-dimethoxyethane (10.0ml). After the addition was complete the mixture was stirred and heated under reflux with the exclusion of atmospheric moisture for 15min.

The resulting orange-red solution was poured carefully on to ice (20g) and the mixture extracted several times with dichloromethane to give 1-phenyl-3-(1-ethyl-2-methyl-4-nitro-1H-imidazol-5-yl)propane-1,2-dione (269) as a light brown solid (0.58g; 96%), mp 160-162°C, which was identified by comparison (mp and IR spectrum) with a sample obtained before.

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